PCT/DK 03/00575
10/526208

#2

Kongeriget Danmark

Patent application No.: PA 2002 01310

Date of filing: 5 September 2002

Applicant: (Name and address)
NeuroSearch A/S
93 Pederstrupvej
DK-2750 Ballerup
Denmark

Title: Diarylurea derivatives and their use as chloride channel blockers

IPC: -

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Patent- og Varemærkestyrelsen
Økonomi- og Erhvervsministeriet

24 September 2003

Pia Høybye-Olsen

PATENT- OG VAREMÆRKESTYRELSEN

DIARYLUREA DERIVATIVES AND THEIR USE AS CHLORIDE CHANNEL BLOCKERS

TECHNICAL FIELD

The present invention relates to novel diarylurea derivatives useful as chloride channel blockers.

In other aspects the invention relates to the use of these compounds in a method for therapy, such as for the treatment of bone metabolic diseases, and to pharmaceutical compositions comprising the compounds of the invention.

BACKGROUND ART

Chloride channels serve a wide variety of specific cellular functions and contribute to the normal function of i.a. skeletal and smooth muscle cells. Chloride channels are probably found in every cell, from bacteria to mammals. Their physiological tasks range from cell volume regulation to stabilization of the membrane potential, transepithelial or transcellular transport and acidification of intracellular organelles.

WO 97/45400, WO 98/47879, WO 00/20378 and WO 00/24707 (all NeuroSearch A/S) describe compounds, such as substituted phenyl derivatives, active as chloride channel blockers.

However, there is a strong interest in the provision of more effective and selective compounds with fewer side effects for the treatment of patients with an osteoclast related bone disease, such as osteoporosis.

SUMMARY OF THE INVENTION

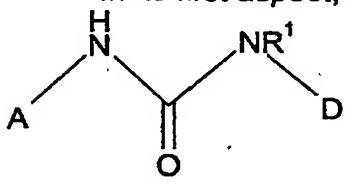
It is an object of the invention to provide novel compounds which act as chloride channel blockers.

A further object of the invention is the provision of compounds with a better selectivity. A still further object is the provision of compounds with a better potency.

A further object of the invention is the provision of compounds that act on cell or tissue specific chloride channels, such as such as chloride channels of osteoclasts. A still further object is the provision of compounds that act on specific groups or subtypes of chloride channels.

A still further object is the provision of compound with more optimal pharmacodynamic properties such as kinetic behaviour, bioavailability, solubility and efficacy.

In its first aspect, the invention provides a compound of general formula I,



(I)

or a pharmaceutically acceptable salt thereof, wherein A, R^1, and D are as defined below.

In its second aspect, the invention provides a pharmaceutical composition, comprising a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

In a further aspect, the invention provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to the blockade of chloride channels.

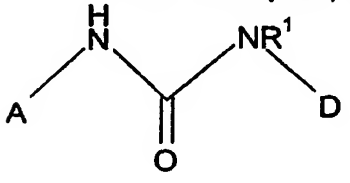
In a still further aspect, the invention relates to a method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to responsive to blockade of chloride channels, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

DETAILED DISCLOSURE OF THE INVENTION

Diarylurea derivatives

In its first aspect, the invention provides a compound of general formula I,



(I)

or a pharmaceutically acceptable salt thereof, wherein

A represents a ring system selected from the group consisting of:

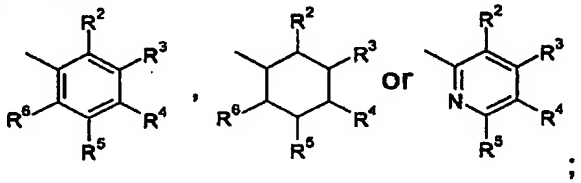
cyclohexanyl, phenyl, pyridyl, thienyl, thiazolyl, naphthyl, indolyl, pyrazolyl and oxo-pyrrolidinyl;

which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:

halogen, trifluoromethyl, nitro, alkyl, alkoxy, and phenyl; and

R^1 represents -H; and

D represents



;

wherein

one of R^2, R^3, and R^4 is selected from the group consisting of:

tetrazolyl, $-COOR^a$, $-B(OH)_2$, $-PO(OR^a)_2$, $-CH_2-PO(OR^a)_2$, and -CONH;

wherein R^a is hydrogen or alkyl:

or R^2 and R^3 or R^3 and R^4 both represent fluoro; and

R^5, R^6 and the remaining one or two of R^2, R^3 and R^4 independently of each other represent:

- hydrogen, halogen, trifluoromethyl,
- $-CH=CH-COOR^b$, $-CH_2-CH_2-COOR^b$,
- $-CO-NR^b-CH_2-COOR^c$; $-CO-NR^bR^c$,
- $-CH=CH-CO-NR^bR^c$; $-CH_2-CH_2-CO-NR^bR^c$,
- piperidylcarbonyl,
- $-NH-CO-R^d$ or $-NH-CO-NH-R^d$;

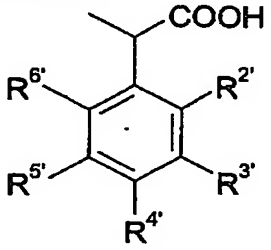
  wherein R^d is phenyl optionally substituted with one or more substituents independently selected from halogen or trifluoromethyl; or
- phenyl optionally substituted with

  $-SO_2-NR^bR^c$, $-CO-NR^bR^c$, $-CO-NR^b-CH_2-COOR^c$, or piperidylcarbonyl;

wherein R^b and R^c independently are hydrogen or alkyl;

or R^1 represents -H; and

D represents



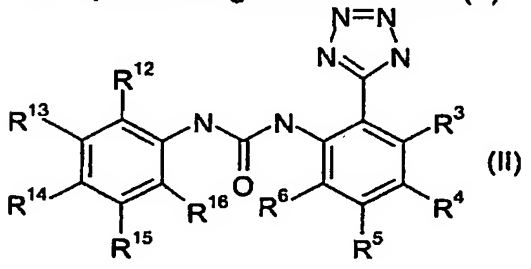
wherein $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, $R^{6'}$ independently of each other represent hydrogen, halogen, or trifluoromethyl:
or R^1 together with D forms $-CHR^e-CH_2-CHR^f-CH_2-$;
wherein R^e represents -COOH;
R^f represents hydrogen or hydroxy.

In one embodiment of the compound of general formula I, one of R^2, R^3 and R^4 represents tetrazolyl, such as 1H-tetrazol-5-yl. In a special embodiment, R^2 represents tetrazolyl, such as 1H-tetrazol-5-yl. In a further special embodiment, R^3 represents tetrazolyl, such as 1H-tetrazol-5-yl. In a further special embodiment, R^4 represents tetrazolyl, such as 1H-tetrazol-5-yl. In a further embodiment of the compound of general formula I, R^2 represents halogen, such as bromo. In a further embodiment of the compound of general formula I, R^2 and R^3 both represent halogen, such as bromo.

In a further embodiment of the compound of general formula I, A is selected from the group consisting of: 1H-indol-2-yl, cyclohexyl, napthyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, thiophen-2-yl, thiazol-2-yl, thiazol-3-yl, 2H-1λ^4-thiazol-2-yl, 3,6-dichloro-pyridin-4-yl, 2,6-dichloro-pyridin-4-yl, 5-chloro-pyridin-2-yl, 2-chloro-pyridin-3-yl, 5-phenyl-2H-pyrazol-3-yl, and 5-oxo-1-phenyl-pyrrolidin-3-yl.

In a further embodiment of the compound of general formula I, A is selected from the group consisting of: phenyl, 2-chloro-phenyl, 2-fluoro-phenyl, 2-bromo-phenyl, 2-methoxy-phenyl, 2-trifluoromethyl-phenyl, 2,3-dichloro-phenyl, 2,4,6-trichloro-phenyl, 2,6-dichloro-phenyl, 3-bromo-phenyl, 3-chloro-phenyl, 3-iodo-phenyl, 3-methoxy-phenyl, 3-nitro-phenyl, 3,4-dichloro-phenyl, 3-fluoro-4-chloro-phenyl, 3-nitro-4-chloro-phenyl, 3-trifluoromethyl-4-chloro-phenyl, 3-trifluoromethyl-4-fluoro-phenyl, 3,5-dichloro-phenyl, 3,5-difluoro-phenyl, 3-fluoro-5-trifluoromethyl-phenyl, 3,5-dimethyl-phenyl, 3,5-dimethoxy-phenyl, 3,5-bis-trifluoromethyl-phenyl, 4-chloro-phenyl, 4-methoxy-phenyl, 4-butoxy-phenyl, and 4-phenyl-phenyl.

In a further embodiment of the compound of general formula I, the compound is a compound of general formula (II)



(II)

or a pharmaceutically acceptable salt thereof, wherein
R^3, R^4, R^5 and R^6 independently of each other represent:

- hydrogen, halogen, trifluoromethyl,
- $-CH=CH-COOR^b$, $-CH_2-CH_2-COOR^b$,
- $-CO-NR^b-CH_2-COOR^c$; $-CO-NR^bR^c$,
- $-CH=CH-CO-NR^bR^c$; $-CH_2-CH_2-CO-NR^bR^c$,
- piperidylcarbonyl,
- $-NH-CO-R^d$ or $-NH-CO-NH-R^d$;
  wherein R^d is phenyl optionally substituted with one or more substituents independently selected from halogen or trifluoromethyl; or
- phenyl optionally substituted with
  $-SO_2-NR^bR^c$, $-CO-NR^bR^c$, $-CO-NR^b-CH_2-COOR^c$, or piperidylcarbonyl;

wherein R^b and R^c independently are hydrogen or alkyl; and
R^{12}, R^{13}, R^{14}, R^{15}, and R^6 independently of each other represent hydrogen, halogen, trifluoromethyl, nitro, alkyl, or alkoxy.

In one embodiment of the compound of general formula II, R^{12} represents hydrogen. In a further embodiment, R^{12} represents halogen, such as chloro, fluoro, or bromo. In a further embodiment, R^{12} represents alkoxy, such as methoxy. In a further embodiment, R^{12} represents trifluoromethyl.

In a further embodiment of the compound of general formula II, R^{13} represents halogen, such as chlorine, fluorine, bromine or iodine. In a further embodiment, R^{13} represents trifluoromethyl. In a further embodiment, R^{13} represents alkoxy, such as methoxy. In a further embodiment, R^{13} represents nitro. In a further embodiment, R^{13} represents alkyl, such as methyl. In a further embodiment, R^{13} represents hydrogen.

In a further embodiment of the compound of general formula II, R^{14} represents halogen, such as chloro. In a further embodiment, R^{14} represents hydrogen. In a further embodiment, R^{14} represents alkoxy, such as methoxy or butoxy. In a further embodiment, R^{14} represents phenyl.

In a further embodiment of the compound of general formula II, R^{15} represents halogen, such as fluorine or chlorine. In a further embodiment, R^{15} represents trifluoromethyl. In a further embodiment, R^{15} represents hydrogen. In a further embodiment, R^{15} represents trifluoromethyl.

In a further embodiment of the compound of general formula II, R^{16} represents hydrogen. In a further embodiment of the compound of general formula II, R^{16} represents halogen, such as chlorine.

In a further embodiment of the compound of general formula II, R^{12}, R^{14} and R^{16} each represents hydrogen. In a further embodiment of the compound of general formula II, R^{12}, R^{15} and R^{16} each represents hydrogen.

In a further embodiment of the compound of general formula II, R^5 represents halogen, such as chlorine, and R^2, R^3, R^4 and R^6 each represent hydrogen.

In a still further embodiment of the compound of general formula II, R^4 and R^6 each represent halogen, such as bromine or chlorine, and R^2, R^3, and R^5 each represent hydrogen. In a special embodiment R^4 and R^6 each represent bromine. In a further special embodiment R^4 and R^6 each represent chlorine.

In a further embodiment of the compound of general formula II, R^4 represents $-CO-NR^bR^c$, such as $-CO-NHCH_3$, $-CO-N(CH_3)_2$ or $-CO-N(CH_2CH_3)_2$, and R^2, R^3, R^5 and R^6 each represent hydrogen.

In a further embodiment of the compound of general formula II, R^4 represents $-CO-NR^b-CH_2-COOR^c$, such as $-CO-NH-CH_2-COOH$, and R^2, R^3, R^5 and R^6 each represent hydrogen.

In a further embodiment of the compound of general formula II, R^4 represents $-CH=CH-COOR^b$, such as $-CH=CH-COOH$, and R^2, R^3, R^5 and R^6 each represent hydrogen.

In a further embodiment of the compound of general formula II, R^4 represents $-CH_2-CH_2-COOR^b$, such as $-CH_2-CH_2-COOH$, and R^2, R^3, R^5 and R^6 each represent hydrogen.

In a further embodiment of the compound of general formula II, R^4 represents $-CH_2-CH_2-CO-NR^bR^c$, such as $-CH_2-CH_2-CO-NHCH_3$, and R^2, R^3, R^5 and R^6 each represent hydrogen.

In a further embodiment of the compound of general formula II, R^4 represents $-CH=CH-CO-NR^bR^c$, such as $-CH=CH-CO-N(CH_3)_2$ or $-CH=CH-CO-NHCH_3$, and R^2, R^3, R^5 and R^6 each represent hydrogen.

In a further embodiment of the compound of general formula II, R^4 represents piperidylcarbonyl, such as 1-piperidylcarbonyl, and R^2, R^3, R^5 and R^6 each represent hydrogen.

In a further embodiment of the compound of general formula II, R^4 represents phenyl substituted with $-SO_2-NR^bR^c$, such as $-SO_2N(CH_3)_2$, and R^2, R^3, R^5 and R^6 each represent hydrogen. In a special embodiment, R4 represents 4-(N,N-dimethyl-sulfamoyl)-phenyl.

In a still further embodiment of the compound of general formula II, R^4 represents phenyl substituted with $-CO-NR^bR^c$, such as $-CO-N(CH_3)_2$, $-CO-NHCH_3$ or $-CO-NH_2$, and R^2, R^3, R^5 and R^6 each represent hydrogen. In a special embodiment, R^4 represents 4-(N,N-dimethyl-carbamoyl)-phenyl, 4-(N-methyl-carbamoyl)-phenyl or 4-carbamoyl-phenyl.

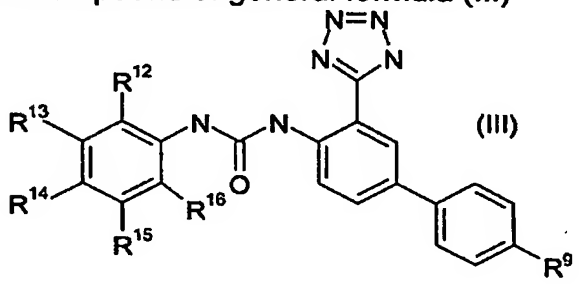
In a still further embodiment of the compound of general formula II, R^4 represents phenyl substituted with $-CO-NR^b-CH_2-COOR^c$, such as $-CO-NH-CH_2-COOH$ or $-CO-N(CH_3)-CH_2-COOH$, and R^2, R^3, R^5 and R^6 each represent hydrogen.

In a still further embodiment of the compound of general formula II, R^4 represents phenyl substituted with piperidylcarbonyl, such as 1-piperidylcarbonyl, and R^2, R^3, R^5 and R^6 each represent hydrogen.

In a still further embodiment of the compound of general formula II, R^4 represents -NH-CO-R^d, such as -NH-CO-phenyl, and R^2, R^3, R^5 and R^6 each represent hydrogen.

In a still further embodiment of the compound of general formula II, R^4 represents -NH-CO-NH-R^d; such as -NH-CO-NH-(3,5-bis-trifluoromethylpheny), and R^2, R^3, R^5 and R^6 each represent hydrogen.

In a further embodiment of the compound of general formula I, the compound is a compound of general formula (III)



(III)

or a pharmaceutically acceptable salt thereof, wherein

R^9 represents -CO-NR^bR^c, -CO-NR^b-CH_2-$COOR^c$, or piperidylcarbonyl;

wherein R^b and R^c independently are hydrogen or alkyl;

two of R^{12}, R^{13}, R^{14}, R^{15}, and R^{16} independently of each other represent halogen, trifluoromethyl, nitro, alkyl, or alkoxy;

and the remaining three of R^{12}, R^{13}, R^{14}, R^{15}, and R^{16} represent hydrogen.

In one embodiment of the compound of general formula III, R^{13} and R^{15} represent trifluoromethyl and R^{12}, R^{14} and R^{16} each represents hydrogen.

In a second embodiment of the compound of general formula III, R^{13} and R^{15} represent halogen, such as chlorine or fluorine, and R^{12}, R^{14} and R^{16} each represents hydrogen.

In a further embodiment of the compound of general formula III, R^{13} and R^{14} represent halogen, such as chlorine, or trifluoromethyl, and R^{12}, R^{15} and R^{16} each represents hydrogen. In a special embodiment, R^{13} represents trifluoromethyl and R^{14} represents chlorine. In a further special embodiment, R^{13} represents chlorine and R^{14} represents trifluoromethyl.

In a further embodiment of the compound of general formula III, R^9 represents -CO-NR^bR^c, such as -CO-NH_2 or -CO-$N(CH_3)_2$.

In a further embodiment of the compound of general formula III, R^9 represents -CO-NR^b-CH_2-$COOR^c$, such as -CO-NH_2-CH_2-COOH or -CO-$NHCH_3$-CH_2-COOH.

In a further embodiment of the compound of general formula III, R^9 represents piperidylcarbonyl, such as 1-piperidylcarbonyl.

In a further embodiment of the compound of general formula I,

A represents a ring system selected from the group consisting of:

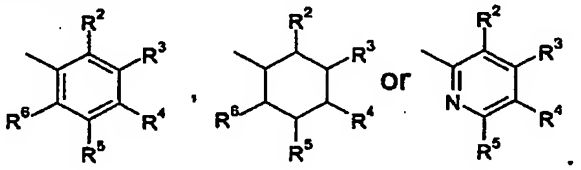
cyclohexanyl, phenyl, pyridyl, thienyl, thiazolyl, and pyrazolyl;

which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:

halogen, trifluoromethyl, nitro, alkyl, alkoxy, and phenyl; and

R^1 represents -H; and

D represents



;

wherein

R^2 represents $-COOR^a$;

wherein R^a is hydrogen or alkyl;

R^3, R^4, R^5, and R^6 independently of each other represent:

- hydrogen, halogen, trifluoromethyl,
- $-NH-CO-R^d$ or $-NH-CO-NH-R^d$;
  wherein R^d is phenyl optionally substituted with one or more substituents independently selected from halogen or trifluoromethyl; or
- phenyl optionally substituted with
  $-SO_2-NR^bR^c$, $-CO-NR^bR^c$, $-CO-NR^b-CH_2-COOR^c$, or piperidylcarbonyl;

wherein R^b and R^c independently are hydrogen or alkyl.

In one embodiment of D, R^5 represents halogen, such as chlorine, bromine or iodine, and R^3, R^4, and R^6 each represent hydrogen.

In a second embodiment of D, R^4 represents halogen, such as bromine or chlorine, and R^3, R^5, and R^6 each represent hydrogen.

In a further embodiment of D, R^3, R^4, R^5, and R^6 each represent hydrogen.

In a further embodiment of D, R^4 and R^6 represent halogen, such as bromine or chlorine, and R^3 and R^5 represent hydrogen.

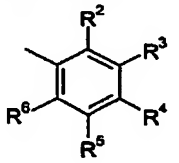
In a further embodiment of D, R^2 represents -COOH or $-COOCH_3$.

In a further embodiment of D, R^4 represents phenyl, and R^3, R^5, and R^6 each represent hydrogen.

In a further embodiment of D, R^5 represents phenyl, and R^3, R^4, and R^6 each represent hydrogen.

In a special embodiment, D represents 2-carboxyphenyl, 2-carboxy-4-bromophenyl, 2-carboxy-4-chlorophenyl, 2-carboxy-4-phenylphenyl, 2-carboxy-4,6-dichlorophenyl, 2-carboxy-5-chlorophenyl, 2-carboxy-5-iodophenyl, 2-carboxy-5-phenylphenyl, 2-carboxycyclohexyl, 3-carboxypyridin-2-yl, 3-carboxy-5-bromopyridin-2-yl, 2-methoxycarbonyl-5-chlorophenyl, or 2-methoxycarbonyl-4-bromorophenyl.

In a further embodiment of the compound of general formula I,
A represents a phenyl optionally substituted with one or more substituents independently selected from the group consisting of
halogen and trifluoromethyl; and
D represents



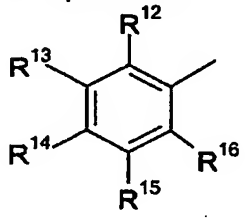
;

wherein
R^3 represents -$COOR^a$;
wherein R^a is hydrogen or alkyl;
R^2, R^4, R^5, and R^6 independently of each other represent

- hydrogen, halogen, or trifluoromethyl; or
- -NH-CO-NH-R^d;
  wherein R^d is phenyl optionally substituted with one or more substituents independently selected from halogen or trifluoromethyl.

In a special embodiment, D represents 2,5-chloro-3-carboxyphenyl, 3-carboxy-5-trifluoromethylphenyl, 3-carboxy-5-(3-bromo-phenylureido)-phenyl, or 3-carboxy-5-(3,5-dichloro-phenylureido)-phenyl.

In a further embodiment of the compound of general formula I,
A represents



wherein R^{12}, R^{13}, R^{14}, R^{15}, and R^{16} independently of each other represent:
halogen, trifluoromethyl, nitro, alkyl, alkoxy, or phenyl.
In a special embodiment R^{13} and R^{15} represent trifluoromethyl and R^{12}, R^{14}, and R^{16} each represent hydrogen.

In a further embodiment of the compound of general formula I,

A represents a ring system selected from the group consisting of:

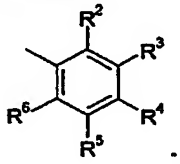
cyclohexanyl, phenyl, and pyridyl;

which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:

halogen, trifluoromethyl, nitro, alkyl, and alkoxy; and

R^1 represents -H; and

D represents



;

wherein

R^2 represents $-B(OH)_2$, $-PO(OR^a)_2$, $-CH_2-PO(OR^a)_2$, or -CONH;

wherein R^a is hydrogen or alkyl (hydrogen, methyl, ethyl);

R^2, R^3, R^4, R^5, and R^6 independently of each other represent:

hydrogen, halogen, trifluoromethyl, or phenyl.

In one embodiment of D, R^2 represents $-B(OH)_2$. In a second embodiment I D, R^2 represents $-PO(OR^a)_2$. In a further embodiment of D, R^2 represents $-CH_2-PO(OR^a)_2$. In a further embodiment of D, R^2 represents -CONH.

In a further embodiment of D, R^3, R^4, R^5, and R^6 each represent hydrogen.

In a special embodiment, D represents 2-dihydroborylphenyl, 2-phosphonophenyl, 2-phosphonomethylphenyl, 2-phosphono-4-bromophenyl, 2-phosphonomethyl-4-bromophenyl, 2-phosphonomethyl-4-chlorophenyl, 2-diethylphosphonophenyl, 2-dimethylphosphonomethylphenyl, 2-dimethylphosphonomethyl-4-chlorophenyl, or 2-diethylphosphono-4-bromophenyl.

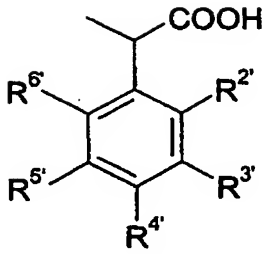
In a further embodiment of the compound of general formula I,

A represents phenyl optionally substituted with one or more substituents independently selected from the group consisting of:

halogen, trifluoromethyl, nitro, alkyl, and alkoxy;

R^1 represents -H; and

D represents



wherein $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, $R^{6'}$ independently of each other represent hydrogen, halogen, or trifluoromethyl.

In a special embodiment, D represents α-carboxy-4-fluorobenzyl or α-carboxy-4-trifluoromethylbenzyl.

In a further embodiment of the compound of general formula I,

A represents a ring system selected from the group consisting of:

cyclohexanyl, phenyl, and pyridyl;

which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:

halogen, trifluoromethyl, nitro, alkyl, and alkoxy; and

R^1 together with D forms $-CHR^e-CH_2-CHR^f-CH_2-$;

wherein R^e represents -COOH;

R^f represents hydrogen or hydroxy.

In one embodiment, R^f represents hydrogen. In a second embodiment, R^f represents hydroxy.

In a further embodiment of the compound of general formula I,

A represents a ring system selected from the group consisting of:

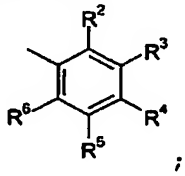
cyclohexanyl, phenyl, and pyridyl;

which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:

halogen, trifluoromethyl, nitro, alkyl, and alkoxy;

R^1 represents -H; and

D represents



;

wherein

R^2 and R^3 or R^3 and R^4 both represent fluoro; and

R^5, R^6 and the remaining one or two of R^2, R^3 and R^4 independently of each other represent hydrogen, halogen, or trifluoromethyl.

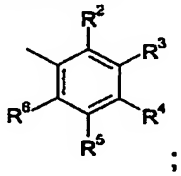
In one embodiment of D, R^2 and R^3 both represent fluoro.

In a second embodiment, R^4, R^5 and R^6 each represent hydrogen.

In a further embodiment, R^4 represents trifluoromethyl and R^5 and R^6 represent hydrogen.

In a special embodiment, D represents 2,3-difluorophenyl or 2,3-difluoro-4-trifluoromethylphenyl.

In a still further embodiment of the compound of general formula I,
A represents a ring system selected from the group consisting of:
cyclohexanyl, pyridyl, and naphthyl;
which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:
halogen, trifluoromethyl, nitro, alkyl, and alkoxy;
R^1 represents -H; and
D represents



;

wherein
R^2 represents tetrazolyl;
R^3, R^4, R^5, and R^6 independently of each other represent:

- hydrogen, halogen, trifluoromethyl; or
- phenyl substituted with
  $-SO_2-NR^bR^c$, $-CO-NR^bR^c$, $-CO-NR^b-CH_2-COOR^c$, or piperidylcarbonyl;

wherein R^b and R^c independently are hydrogen or alkyl (methyl).

In a special embodiment, A is selected from cyclohexanyl, 2,6-dichloro-pyridin-4-yl, pyridin-3-yl and 3-naphthalen-1-yl; and D is selected from 3-chloro-6-(1H-tetrazol-5-yl)phenyl, 4-bromo-2-1H-tetrazol-5-yl)phenyl, and 4'-(N,N-dimethyl-1-carbonyl)-2-(1H-tetrazol-5-yl)-biphenyl-4-yl.

In a special embodiment the compound of the invention is
N-(3,5-Bis-trifluoromethyl-phenyl)-N´-[2-bromo-4-(1H-tetrazol-5-yl)-phenyl urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N´-[2,6-dibromo-3-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N´-[2-bromo-5-(1H-tetrazol-5-yl)-phenyl] urea;

5-Chloro-2-[3-(1H-indol-2-yl)-ureido]-benzoic acid;
5-Bromo-2-[3-(1H-indol-2-yl)-ureido]-benzoic acid;
N-(3-Fluoro-5-trifluoromethyl-phenyl)-N´-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4´-sulfonic acid-dimethylamide] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N´-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4´-sulfonic acid-dimethylamide] urea;
N-(3,5-Difluoro-phenyl)-N´-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4´-sulfonic acid-dimethylamide] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N´-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N´-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3-Bromo-phenyl)-N´-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-N´-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3-Chloro-phenyl)-N´-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(4-Fluoro-3-trifluoromethyl-phenyl)-N´-[2,4-dibromo-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,4-Dichloro-phenyl)-N´-[2,4-dibromo-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3-Methoxy-phenyl)-N´-[4´-(N´´,N´´-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(2-Methoxy-phenyl)-N´-[4´-(N´´,N´´-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(4-Methoxy-phenyl)-N´-[4´-(N´´,N´´-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(2-Trifluoromethyl-phenyl)-N´-[4´-(N´´,N´´-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N´-[4´-(N´´,N´´-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(3,5-Dichloro-phenyl)-N´-[2,4-dibromo-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(2-Chloro-phenyl)-N´-[4´-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(3,5-Dichloro-phenyl)-N´-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N´-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-N´-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl)-N´-[2,4-dichloro-5-(1H-tetrazol-5yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-N´-[4-(N´´-methyl-carboxamide)- 2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-N´-[4-(N´´-methyl-carboxamide)- 2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N´-[4-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea;

N-(4-Chloro-3-trifluoromethyl-phenyl)-N´-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-N´-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N´-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-N´-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(2-Chloro-phenyl)-N´-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(4-Chloro-3-trifluoro-phenyl)-N´-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-N´-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N´-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-N´-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(2-Chloro-phenyl)-N´-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-N´-[4-(N´´-malonamic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N´-[4-(N-malonamic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-N´-[4-(N´´-malonamic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(2-Chloro-phenyl)-N´-[4-(N´´-malonamic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 158-160°C;
N-(3,5-Bis-trifluoromethyl-phenyl)-N´-{4-[(N´´,N´´-dimethyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl} urea;
N-(3,5-Difluoro-phenyl)-N´-{4-[(N´´,N´´-dimethyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl} urea;
N-(2-Chloro-phenyl)-N´-{4-[(N´´,N´´-dimethyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl} urea;
N-(3,5-Dichloro-phenyl)-N´-{4-[(N´´-methyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl} urea;
N-(3,5-Difluoro-phenyl)-N´-{4-[(N´´-methyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl} urea;
N-(2-Chloro-phenyl)-N´-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-N´-[4-(N´´,N´´-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;

N-(3,5-Bis-trifluoromethyl-phenyl)-N´-[4-(N´´,N´´-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-N´-[4-(N´´,N´´-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(2-Chloro-phenyl)-N´-[4-(N´´,N´´-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N´-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-dichloro-phenyl)-N´-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N´-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-N´-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-N´-[4´-(carbonyl-(N´´-methyl)amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Dichloro-phenyl)-N´-[4-(N´´,N´´-dimethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-N´-[4-(N´´,N´´-dimethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(4-Chloro-3-trifluoromethyl)-N´-[4-(N´´,N´´-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(2-Chloro-phenyl)-N´-[4´-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N´-[4-(N´´-methyl-propylamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-N´-[4-(N´´-methyl-propyamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluromethyl-phenyl)-N´-[4-(N´´-methyl-propylamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-N´-[4-(N´´-methyl-propylamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(2-chloro-phenyl)-N´-[4-(N´´-methyl-propylamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(2,6-Dichloro-phenyl)-N´-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(2,4,6-trichloro-phenyl)-N´-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-N´-[4-benzamide-2-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-N´-[4-benzamide-2-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N´-[4-benzamide-2-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)- N´-[4-benzamide-2-(1H-tetrazol-5-yl)-phenyl) urea;

N-(4-Chloro-3-trifluoromethyl-phenyl)- N′-[4-(N′′,N′′-dimethyl acryl-amide)-2-(1-H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-dichloro-phenyl)-N′-[4-(N′′,N′′-dimethyl acryl-amide)-2-(1-H-tetrazol-5-yl)phenyl] urea;
N-(3-Chloro-4-fluoro-phenyl)-*N*′-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4′-sulfonic acid-dimethylamide] urea;
N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N*′-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4′-sulfonic acid-dimethylamide] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N′-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4′-carboxylic acid dimethylamide] urea;
N-(3,5-Dichloro-phenyl)-N′-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4′-carboxylic acid dimethylamide] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N′-[4′-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(3,5-Dichloro-phenyl)-N′-[4′-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N′-[4′-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(3,5-Difluoro-phenyl)-N′-[4′-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N′-[4′-carboxamide-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Dichloro-phenyl)-N′-[4′-carboxamide-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N′-[4′-carboxamide-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Difluoro-phenyl)-N′-[4′-carboxamide-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Dichloro-phenyl)-N′-[4′-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Difluoro-phenyl)-N′-[4′-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N′-{4′-[carbonyl-(N′′-methyl)-amino-acetic acid]-2-(1H-tetrazol-5-yl)-4-biphenyl} urea;
N-(3,5-Dichloro-phenyl)-N′-{4′-[carbonyl-(N′′-methyl)-amino-acetic acid]-2-(1H-tetrazol-5-yl)-4-biphenyl} urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N′-{4′-[carbonyl-(N′′-methyl)-amino-acetic acid]-2-(1H-tetrazol-5-yl)-4-biphenyl} urea;
N-(3,5-Difluoro-phenyl)-N′-[4′-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;

N-(3,5-Bis-trifluoromethyl-phenyl)-N′-[4′-(N′′-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N′-[4′-(N′′-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
4-Chloro-2-(3-cyclohexyl-ureido)-benzoic acid;
5-Bromo-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]-benzoic acid;
2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-cyclohexanecarboxylic acid;
5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3-bromo-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]-benzoic acid;
N-(3,5-Bis-trifluormethyl-phenyl)-N′-(phenyl-2-boronic acid) urea;
N-(4-Chloro-3-fluoro-phenyl)-N′-(phenyl-2-boronic acid) urea;
N-(3,5-Dichloro-phenyl)-N′-(phenyl-2-boronic acid) urea;
N-Cyclohexyl-N′-(phenyl-2-boronic acid) urea;
5-Chloro-2-[3-(pyridin-3-yl)-ureido]-benzoic acid;
5-Bromo-2-[3-(pyridin-3-yl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(3-chloro-4-fluoro-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(4-fluoro-3-trifluoromethyl-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(3-fluoro-5-trifluoromethyl-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(3,5-difluoro-phenyl)-ureido]-benzoic acid;
2-[3-(Thiophen-2-yl)-ureido]-benzoic acid;
2-[3-(Pyridin-4-yl)-ureido]-benzoic acid;
4-Chloro-2-[3-(pyridin-4-yl)-ureido]-benzoic acid;
5-Bromo-2-[3-(pyridin-4-yl)-ureido]-benzoic acid;
2-[3-(Pyridin-3-yl)-ureido]-nicotinic acid;
2-[(3-(3-Chloro-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-[(3-(3-Bromo-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-[3-(3,5-Dichloro-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-(3-Cyclohexyl-ureido)-cyclohexanecarboxylic acid;
2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-cyclohexane carboxylic acid;
4-Chloro-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3-chloro-phenyl)-ureido]-benzoic acid;
2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-nicotinic acid;
5-Bromo-2-(3-cyclohexyl-ureido)-benzoic acid;
2-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-cyclohexanecarboxylic acid;

2-[3-(3-Chloro-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-[3-(3-Bromo-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-[3-(2,6-Dichloro-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-cyclohexanecarboxylic acid;
4-Chloro-2-[3-(thiazol-2-yl)-ureido]-benzoic acid methyl ester;
5-Bromo-2-[3-(pyridin-2-yl)-ureido]-benzoic acid methyl ester;
4-Chloro-2-[3-(5-chloro-pyridin-2-yl)-ureido]benzoic acid;
5-Bromo-2-(3-thiazol-2-yl-ureido)-benzoic acid methyl ester;
2-[3-(5-Bromo-pyridin-3-yl)-ureido]-4-chloro-benzoic acid;
5-Bromo-2-[3-(pyridin-2-yl)-ureido]-benzoic acid;
3-Bromo-2-[3-(2H-1λ^4-thiazol-2-yl)-ureido]-benzoic acid;
3-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
4-[3-(3,5-Dichloro-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-[3-(3,5-Difluoro-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-[3-(2-Chloro-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-Chloro-2-[3-(5-phenyl-2H-pyrazol-3-yl)-ureido]-benzoic acid;
2-[3-(2-chloro-pyridin-3-yl)-ureido]-nicotinic acid;
4-Chloro-2-[3-(2-chloro-pyridin-3-yl)-ureido]-benzoic acid;
2-[3-(4-Chloro-phenyl)-ureido]-5-iodo-benzoic acid;
5-Chloro-2-[3-(5-oxo-1-phenyl-pyrrolidin-3-yl)-ureido]-benzoic acid;
5-Bromo-2-(3-phenyl-ureido)-benzoic acid;
5-Bromo-2-[3-(2-fluoro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(2-chloro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3,5-dimethyl-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3,5-difluoro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3,5-dimethoxy-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(2,6-dichloro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(2-bromo-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(4-chloro-3-nitro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(4-butoxide-phenyl)-ureido]-benzoic acid;
5-Chloro-2-[3-(2-chloro-phenyl)-ureido]-benzoic acid;
5-Chloro-2-[3-(3,5-dimethyl-phenyl)-ureido]-benzoic acid;
2-[3-(4-Biphenyl)-ureido]-5-bromo-benzoic acid;
5-Chloro-2-[3-(3-iodo-phenyl)-ureido]- -benzoic acid;
5-Chloro-2-(3-phenyl-ureido)-benzoic acid;
5-Chloro-2-[3-(2-fluoro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-nicotinic acid;
5-Bromo-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]-nicotinic acid;

5-Chloro-2-[3-(3,5-difluoro-phenyl)-ureido]-benzoic acid;
5-Chloro-2-[3-(3,5-dimethoxy-phenyl)-ureido]-benzoic acid;
5-Chloro-2-[3,4-dichloro-phenyl)-ureido]-benzoic acid;
2-[3-(4-Butoxy-phenyl)-ureido]-5-chloro- benzoic acid;
5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]-nicotinic acid;
3,5-Bis-[3-(3,5-difluro-phenyl)-ureido]- benzoic acid;
5-Bromo-2-[3-(3,5-difluoro-phenyl)-ureido]-nicotinic acid;
5-Bromo-2-[3-(2,4,6-trichloro-phenyl)-ureido]-nicotinic acid;
5-Chloro-2-[3-(2,6-dichloro-phenyl)-ureido]-benzoic acid;
2,5-Dichloro-3-[3-(3-bromo-phenyl)-ureido]-benzoic acid;
2,5-Dichloro-3-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid;
3,5-Bis-[3-(3-bromo-phenyl)-ureido]- benzoic acid
3,5-Bis-[3-(3,5-dichloro-phenyl)-ureido]- benzoic acid;
3-[3-(3-Bromo-phenyl)-ureido]-5-trifluoro-benzoic acid;
3-[3-(3,5-Dichloro-phenyl)-ureido]-5-trifluoro-benzoic acid;
3,5-Bis-[3-(3,5-bis-trifluoromethylphenyl)-ureido]- benzoic acid;
2-[3-(Pyridin-3-yl)-ureido]-phenyl-boronic acid;
2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-phenyl-boronic acid;
2-[3-(3-Bromo-phenyl)-ureido]-phenyl-dihydroxy-borane;
{2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid;
{2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid
{2-[3-(3-chloro-phenyl)-ureido]-phenyl}-phosphonic acid diethyl ester;
{2-[3-(3-chloro-phenyl)-ureido]phenyl}-phosphonic acid;
{2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid;
{2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid;
{5-Bromo-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{5-Bromo-2-[3-(3,5 bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid;
{5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid;
{5-Bromo-2-[3-(3-chloro-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{5-Bromo-2-[3-(3-chloro-phenyl)-ureido]phenyl}-phosphonic acid;
{5-Bromo-2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{5-Bromo-2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid;

{5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid;
{5-Bromo-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]phenyl}-phosphonic acid diethyl ester;
{5-Bromo-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]phenyl}-phosphonic acid;
2-{[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
2-{[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid;
2-{[3-(3,5-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
2-{[3-(3,5-Dichloro-phenyl)-ureido]-benzyl}-phosphonic acid;
2-[(3-Phenyl-ureido)-benzyl]-phsophonic acid dimethyl ester;
2-[(3-Phenyl-ureido)-benzyl]-phsophonic acid;
2-[3-(4-Chloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
2-[3-(4-Chloro-phenyl)-ureido]-benzyl}-phosphonic acid;
2-{[3-(3,4-Dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
2-{[3-(3,4-Dichloro-phenyl)-ureido]-benzyl}-phosphonic acid;
{5-Chloro-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
{5-Chloro-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid;
{5-Chloro-2-[3-(3,5-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
{5-Chloro-2-[3-(3,5-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid;
[5-Chloro-2-(3-phenyl-ureido)-benzyl]-phosphonic acid dimethyl ester;
[5-Chloro-2-(3-phenyl-ureido)-benzyl]-phosphonic acid;
{5-Chloro-2-[3-(3,4-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
{5-Chloro-2-[3-(4-chloro-phenyl)-ureido]-benzyl}-phosphonic acid;
{5-Chloro-2-[3-(3,4-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
{5-Chloro-2-[3-(3,4-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid;
{2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-phenyl}-phosphonic acid diethyl ester;
{2-[3-(2-Trifluoromethyl-phenyl)-ureido]-phenyl}-phosphonic acid diethyl ester;
{2-[3-(2-Trifluoromethyl-phenyl)-ureido]-phenyl}-phosphonic acid;
3-[3-(3,5-Dichloro-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
3-[3-(2,3-Dichloro-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
3-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
{2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-phenyl}-phosphonic acid;
[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-(5-trifluoromethyl-phenyl)-acetic acid;
[3-(4-Chloro-3-fluoro-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
[3-(3,5-Dichloro-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
[3-(3-Chloro-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
1-(3,5-Bis-trifluoromethyl-phenylcarbamoyl)-pyrroline-2-carboxylic acid;

1-(3,5-Bis-trifluoromethyl-phenylcarbamoyl)-4-hydroxy-pyrroline-2-carboxylic acid;
1-(4-Chloro-3-trifluoromethyl-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid;
1-(3-Chloro-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid;
1-(3-Bromo-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid;
1-(3,5-Dichloro-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid;
1-(Cyclohexyl-carbamoyl)-pyrrolidine-2-carboxylic acid;
1-(2,6-Dichloro-pyridin-4-ylcarbamoyl)-pyrrolidine-2-carboxylic acid;
1-(4-Chloro-3-trifluoromethyl-phenylcarbamoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid;
1-(3-Chloro-phenylcarbamoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid;
1-(3-Bromo-phenylcarbamoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid;
1-(Pyridin-3-ylcarbamoyl)-pyrrolidine-2-carboxylic acid;
N-Cyclohexyl-N′-(2,3-difluoro-4-trifluoromethyl-phenyl) urea;
N-Cyclohexyl-N′-(2,3-difluoro-phenyl) urea;
N-(2,3-Difluoro-4-trifluoromethyl-phenyl)-N′-(pyridin-3-yl) urea;
N-(Pyridin-3-yl)-N′-(2,3-difluoro-phenyl) urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N′-(2,3-difluoro-4-trifluoromethyl-phenyl) urea;
N-(2,6-Dichloro-pyridin-4-yl)-N′-(2,3-difluoro-4-trifluoromethyl-phenyl) urea;
N-(2,3-Difluoro-4-trifluoromehyl-phenyl)-N′-(pyridin-4-yl) urea;
N-(2,3-Difluoro-phenyl)-N′-(pyridin-4-yl) urea;
N-(Cyclohexyl)-N′-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(2,6-Dichlooro-pyridin-4-yl)-N′-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-Cyclohexyl-N′-[4′-(N′′,N′′-dimethyl-1-carbonyl)-2-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(2,6-Dichloro-pyridin-4-yl)-N′-[4′-(N′′,N′′-dimethyl-1-carbonyl)-2-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-Cyclohexyl-N′-[4-bromo-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(2,6-Dichloro-pyridin-4-yl)-N′-[4-bromo-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-[5-Chloro-2-(1H-tetrazol-5-yl)-phenyl]-N′-(pyridin-3-yl) urea;
N-[4-Bromo-2-(1H-tetrazol-5-yl)-phenyl]-N′-(pyridin-3-yl) urea;
N-(Naphthalen-1-yl)-N′-[4′-(N′′,N′′-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-[2,4-Dibromo-6-(1H-tetrazol-5-yl)-phenyl]-N′-(2,6-dichloro-pyridin-4-yl) urea;
or a pharmaceutically acceptable salt thereof.

Definition of Substituents

In the context of this invention halogen represents a fluorine, a chlorine, a bromine or an iodine atom.

Alkyl means a straight chain or branched chain of one to six carbon atoms, including but not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, and hexyl; methyl, ethyl, propyl and isopropyl are preferred groups.

Alkoxy is O-alkyl, wherein alkyl is as defined above.

Amino is NH_2 or NH-alkyl or N-$(alkyl)_2$, wherein alkyl is as defined above.

Steric Isomers

The chemical compounds of the present invention may exist in (+) and (-) forms as well as in racemic forms. The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the diastereomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example.

The chemical compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the chemical compound of the present invention with an optically active chloroformate or the like.

Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optical active compounds can also be prepared from optical active starting materials.

Pharmaceutically Acceptable Salts

The chemical compound of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention.

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride, the hydrobromide, the nitrate, the perchlorate, the phosphate, the sulphate, the formate, the acetate, the aconate, the ascorbate, the

benzenesulphonate, the benzoate, the cinnamate, the citrate, the embonate, the enantate, the fumarate, the glutamate, the glycolate, the lactate, the maleate, the malonate, the mandelate, the methanesulphonate, the naphthalene-2-sulphonate derived, the phthalate, the salicylate, the sorbate, the stearate, the succinate, the tartrate, the toluene-p-sulphonate, and the like. Such salts may be formed by procedures well known and described in the art.

Metal salts of a chemical compound of the invention include alkali metal salts such as the sodium salt of a chemical compound of the invention containing a carboxy group.

Methods of Preparation

The compounds of the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

Also one compound of the invention can be converted to another compound of the invention using conventional methods.

The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

Pharmaceutical Compositions

In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of a compound of the invention.

While a compound of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising a compound of the invention, or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers therefore, and, optionally, other therapeutic and/or prophylactic ingredients, know and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

The pharmaceutical composition of the invention may be administered by any convenient route, which suit the desired therapy. Preferred routes of administration include oral administration, in particular in tablet, in capsule, in dragé, in powder, or in liquid form, and parenteral administration, in particular cutaneous, subcutaneous,

intramuscular, or intravenous injection. The pharmaceutical composition of the invention can be manufactured by any skilled person by use of standard methods and conventional techniques appropriate to the desired formulation. When desired, compositions adapted to give sustained release of the active ingredient may be employed.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

The actual dosage depend on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 μg/kg i.v. and 1 μg/kg p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 μg/kg to about 10 mg/kg/day i.v., and from about 1 μg/kg to about 100 mg/kg/day p.o.

Biological Activity

The compounds of the present invention are useful as blockers of chloride channels, such as chloride channels of osteoclasts. For measuring the activity of the compounds, various osteoclast inhibition assays known in the art can be used.

Methods of Therapy

Compounds that are active as chloride channels blockers are likely to be useful in the treatment of a number of diseases, disorders and conditions, including bone metabolic diseases.

Thus in a further aspect, the compounds of the invention are considered useful for the treatment, prevention or alleviation of a disease, disorder or condition responsive to the blockade of chloride channels.

In a special embodiment, the disease or a disorder or a condition is a bone metabolic disease, such as an osteoclast related bone disease. In a further embodiment, the disease or a disorder or a condition is an osteoclast related bone disease, such as osteoporosis, postmenopausal osteoporosis, secondary osteoporosis, osteolytic breast cancer bone metastasis, osteolytic cancer invation, and Paget's disease of bone.

It is at present contemplated that suitable dosage ranges are 0.1 to 1000 milligrams daily, 10-500 milligrams daily, and especially 30-100 milligrams daily, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge. When administered in combination with compounds known in the art for treatment of the diseases, the dosis regimen may be reduced.

Use of the compounds of the invention may be combined with the use of other bone metabolism controlling compounds for the treatment of bone metabolic disease. Such known bone metabolism controlling compounds include bisphophonates such as etidronate, pamidronate, or clodronate optionally combined with calcium; oestrogen-receptor active compounds such as oestrogen i.e. oestradiol and ethyloestradiol, calcitonin, 1,25-dihydroxyvitamine D and metabolites thereof, fluoride, growth hormone, parathyroid hormone, triiodo-thyrosine, collagen degrading enzymes such as protease inhibitors, or cancer therapeutic agents.

The treatment of the diseases and disorder can be in chronical or a long term treatment as well as a treatment of sudden crisis in the disease and disorder.

EXAMPLES

The invention is further illustrated with reference to the following examples, which are not intended to be in any way limiting to the scope of the invention as claimed.

Example 1
(2-Amino-phenyl)-phosphonic acid diethyl ester

Diethylphosphite (1.5 g, 11 mmol) in liquid ammonia (app. 100 ml) was added potassium tert.-butoxide (1.23 g, 11 mmol), the reaction mixture was stirred for 10 min. before 2-iodoaniline was added. The reaction mixture was irradiated (Hg-lamp) for an hour. Ammonia was evaporated and ammonium chloride was added with some ammonia, ammonia was evaporated off. The residue was added water and extracted with dichloromethane. The title compound was purified by column chromatography. Yield 1.7 g (yellow oil).

Example 2
(2-Amino-5-bromo-phenyl)-phosphonic acid diethyl ester

(2-Amino-phenyl)-phosphonic acid diethyl ester (0.23g, 1 mmol) in glacial acetic acid (2 ml) under stirring was added bromine (0.16 g, 1 mmol, 1 eq.) in glacial acetic acid (2 ml) over 20 min. After the reaction was completed, the reaction mixture was poured into a saturated aqueous sodium bicarbonate solution. The title compound was extracted with dichloromethane and purified by column chromatography. Yield 0.23 g

Example 3
[(Dimethoxy-phosphoryl)-hydroxy-(2-nitro-phenyl)-methyl]-phosphonic acid dimethyl ester

Trimethyl phosphite (5.7 g, 45.7 mmol) was cooled to –10°C under a argon atmosphere and glacial acetic acid was added (1.44 ml), while keeping the temperature below 0°C, was drop wise added 2-nitrobenzoyl chloride, the reaction mixture was allowed to heat to room temperature and stirred for one hour. At a pressure of 10 mmHg was the reaction mixture heated to 40°C for one hour and cooled to room temperature. Ethyl acetate was added and the solution was washed with 5% sodium bicarbonate (aq.), the organic phase was dried and evaporated, the title compound was purified by column chromatography.

The following compound was made analogously;
[(Dimethoxy-phosphoryl)-hydoxy-(3-chloro-6-nitro-phenyl)-methyl]-phosphonic acid dimethyl ester.

Example 4
5-Amino-furan-2-carboxylic acid

5-Nitro-2-furoic acid methyl ester (14.3 g, 84 mmol) in ethyl acetate (110 ml) was added palladium on charcoal (0.75 g, 5 %), the solution was stirred at 40°C under a hydrogen atmosphere for 4 hours, the reaction mixture was filtered through celite, the title compound was isolated by evaporation and used as this in the next reaction.

Example 5
4-Amino-1-hydroxy-cyclohexa-2,4-dienecarboxylic acid methyl ester

5-Amino-furan-2-carboxylic acid (the crude product from example 4) was dissolved in benzene (0.5 L) and added acrylonitrile (200 ml), the reaction mixture was heated at

reflux, stirred for 16 hours and evaporated, the residue was added toluene and evaporated. The title compound was crystallized from ethyl acetate, and used with out further purification in the next reaction.

Example 6
4-Amino-3-cyano-benzoic acid methyl ester

4-Amino-1-hydroxy-cyclohexa-2,4-dienecarboxylic acid methyl ester (the crude product from example 5) was dissolved in toluene (600 ml) and added boron trifluoride diethyl etherate (20 ml of 40 % in diethyl ether), the reaction mixture was added tetrahydrofurane (100 ml) and stirred at 85°C for 30 min. The reaction mixture was cooled to room temperature and poured into ice/water, the mixture was neutralized with sodium hydroxide (1 M) and basified with saturated sodium bicarbonate. The layer was separated and the water phase was extracted with dichloro methane. The organic phases was dried and evaporated. The title compound was isolated from the residue by column chromatography. Yield 3.2 g.

Example 7
4-Amino-3-cyano-benzoic acid

4-Amino-3-cyano-benzoic acid methyl ester (3.2 g, 10 mmol) in tetrahydrofurane/ water (110 ml, 1:1) was added lithium hydroxide hydrate (2.3 g, 30 mmol), the reaction mixture was stirred at room temperature for 20 hours and added hydro chloric acid (1 M) to pH = 3. From the mixture was tetrahydrofurane distilled of and the title compound precipitated out of solution.

Example 8
4-Amino-3-cyano-N-methyl-benzamide

4-Amino-3-cyano-benzoic acid (0.97 g, 6 mmol), benzotriazol-1-yloxytris-(pyrrolidino)phosphonium hexafluorophosphate (3.3 g, 6.3 mmol) and diisopropylethylamine (6 ml, 12 mmol) in anhydrous dimethyl formamide (25 ml) was added dimethylamine (6 ml of a 2 M in tetrahydrofurane), the reaction mixture was stirred at room temperature overnight. Some of the dimethylformamide was evaporated off, the crude product was dissolved in ethyl acetate (25 ml), washed with potassium hydrogen sulphate (twice with 0.5 M (25 ml)), sodium hydroxide (twice with 1 M (25 ml)), water (10 ml) and brine (25 ml). The organic layer was dried and evaporated, the title compound was isolated by column chromatography. Yield 0.39 g.

The following compounds were made analogously:
4-Amino.3-cyano-N,N-dimethyl-benzamide;
(4-Amino-3-cyano-benzoylamino)-acetic acid ethyl ester;
2-Amino-5-(piperidine-1-carbonyl)-benzonitrile;
4-Amino-3-cyano-N,N-diethyl-benzamide;
[(4-Amino-3-cyano-benzoyl)-methyl-amino]-acetic acid.

Example 9
(2-Amino-benzyl)-phosphonic acid dimethyl ester

[(Dimethoxy-phosphoryl)-hydroxy-(2-nitro-phenyl)-methyl]-phosphonic acid dimethyl ester (4.7 g, 17.7 mmol) in 99 % ethyl alcohol (40 ml) was added Tin(II) chloride dihydrate (14.4 g, 64 mmol, 5 eq.), the reaction mixture was heated at 70°C for 20 min. and poured into ice (250 ml), pH was adjusted to 7 with sodium hydroxide (1 M) and ethyl acetate was added, the emulsion was filtered through kieselguhr twice, the organic layer was washed with brine, dried, evaporated and the title compound was isolated as an oil. Yield 2 g.

The following compound was made analogously:
(2-Amino-5-chloro-benzyl)-phosphonic acid dimethyl ester.

Example 10
2-Amino-benzeneboronic acid

2-Nitro-benzeneboronic acid (2.32 g, 14 mmol) in ethyl alcohol (130 ml, 99%) was added palladium on charcoal (0.232 g, 10 %), stirred under a hydrogen atmosphere (3 bar) overnight and filtered. The filtrate was evaporated, the title compound was crystallized from methyl alcohol and water. Yield 0.52 g.

Example 11
4-Methyl-phenyl-boronic acid

4-Bromo-toluene (50 g, 0.29 mol) in anhydrous diethyl ether (500 ml) was cooled to -20°C, while keeping the temperature under – 20°C, was butyl lithium (127 ml of an 2.5 M solution in hexane 0.31 mol) added, after 15 min the solution was allowed to heat to 15°C and stirred at that temperature for an hour, then cooled to – 55°C, while keeping the temperature under - 47°C was tributylborate (110 ml, 94 g, 0.41 mol, 1.4 eq.) added, the reaction mixture was allowed to heat to room temperature and stirred overnight. Hydrochloric acid (450 ml of 1 M) was added. The phases was separated,

the water phase was extracted with diethyl ether, the organic phases was combined and extracted with sodium hydroxide (aq.) (300 ml + 2 times with 100ml of 2 M), the water phases was added concentrated hydrochloric acid (app. 100 ml), the title compound precipitated and was isolated by filtration. Yield 32.6 g

Example 12
4-(Dihydroxyboryl) benzoic acid

4-Methyl-phenyl-boronic acid (32.6 g 0.24 mol) was dissolved in water (900 ml) containing sodium hydroxide (19.2 g 0.48 mol, 2 eq.) and added potassium permanganate (79.6 g, 0.5 mol, 2.1 eq.), the reaction mixture was stirred at room temperature for 72 hours and filtered, the precipitate was washed three times with water (50 ml), the filtrate was added concentrated hydrochloric acid (app. 55 ml) and the title compound precipitated. Yield 34.5 g.

Example 13
4-(Dihydroxyboryl)-(N,N-dimethylbenzamide)

4-(Dihydroxyboryl) benzoic acid (34.4 g, 0.21 mol) was added to thionyl chloride (300 ml), the reaction mixture was heated at reflux overnight and evaporated to dryness, the residue was added dimethylamine (167 ml of a 40 % solution in water), the reaction mixture was heated at reflux for 20 min. and filtered while still hot, the filtrate was cooled to room temperature and added concentrated hydrochloric acid and the title compound precipitated. Yield 25.1 g.

The following compounds were made analogously:
4-(Dihydroxyboryl)-benzamide;
[4-(Dihydroxyboryl)-benzoylamino]-acetic aid;
[4-(Dihydroxyboryl)-benzoyl-(N-methyl)-amino]-acetic acid.

Example 14
4´-Amino-3´-cyano-biphenyl-4-carboxylic acid dimethylamide

4-(Dihydroxyboryl)-(N,N-dimethylbenzamide) (1.2 g, 6.2 mmol), 2-amino-5-bromobenzonitrile (1.1 g, 5.6 mmol, 0.9 eq), potassium carbonate (2.3g, 16.9 mmol, 3.3 eq.), dimethoxyethylenglycol (20 ml) and water (10 ml) was mixed nitrogen was bobbled through the mixture, bis(triphenylphosphine)palladium (II) chloride (0.05 g) was added, the reaction mixture was heated at reflux for 40 min, cooled to room temperature, added water (50 ml) and extracted with ethyl acetate (50 ml), the organic

phase was washed with water (30 ml) dried, evaporated and the title compound was left as an oil. Yield 1.17 g.

Example 15

3-(4-Amino-3-cyano-phenyl)-acrylic acid methyl ester

2-Amino-5-bromo-benzonitrile (0.59 g 3 mmol), methylacrylate (0.52 g, 6 mmol) and tri-o-tolylphosphine (0.49 mg, 0. 16 mmol) in anhydrous N,N-dimethyl formamide (5 ml) was added triethylamine (0.44 ml), the mixture was bobbled through with argon and palladium (II) acetate (4.5 mg, 0.02 mmol) and stirred at 120°C for 2.5 hours. Then the reaction was finished, the reaction mixture was cooled to room temperature and added hydrochloric acid (15 ml of 1 M), the title compound was extracted with diethyl ether (four times with 25 ml), the organic phase was dried and evaporated.

The following compound was made analogously:
3-(Amino-3-cyano-phenyl)-acryl N,N-dimethyl amide.

Example 16

3-(4-Amino-3-cyano-phenyl)-propionic acid methyl ester

3-(4-Amino-3-cyano-phenyl)-acrylic acid methyl ester (10 g, 49 mmol) and palladium on charcoal (2 g, 10 %) in tetrahydrofurane (200 ml) was stirred vigorously under a hydrogen atmosphere for 20 min., the reaction mixture was filtered though celite and the title compound was isolated by filtration. Yield 10 g

The following compound was made analogously:
3-(4-Amino-3-cyano-phenyl)-propionic acid N,N-dimethyl amide.

Example 17

4′-Amino-3′-(1H-tetrazol-5-yl)-biphenyl-4-carboxylic acid dimethylamide

4′-Amino-3′-cyano-biphenyl-4-carboxylic acid dimethylamide (1.15 g, 4.3 mmol) in toluene (25 ml) was added sodium azide (0.42 g, 6.5 mmol, 1.5 eq.) and triethylammonium chloride (0.9 g, 6.5 mmol, 1.5 eq.), the reaction mixture was stirred at 60°C for 48 hours. The top phase was decanted from the bottom layer, the residue was added water (25 ml), 96 % ethyl alcohol (25 ml) and concentrated hydro chloric acid (app. 1 ml) and the title compound precipitated out. Yield 0.79 g.

The following compounds were made analogously:

4′-Amino-3-(1H-tetrazol-5-yl)-biphenyl-4-dimethyl-sulfon-amide;
2-Bromo-4-(1H-tetrazol-5-yl)-aniline;
2,6-Dibromo-4-(1H-tetrazol-5-yl)-aniline;
2-Bromo-5-(1H-tetrazol-5-yl)-aniline;
3-Chloro-6-(1H-tetrazol-5-yl)-aniline;
4-Bromo-2-(1H-tetrazol-5-yl)-aniline;
2,4-Dibromo-6-(1H-tetrazol-5-yl)-aniline;
[4′-Amino-3′-(1H-tetrazol-5-yl)-biphenyl-4-yl)-carbonyl-piperidin-1-yl;
2,4-Dihcloro-6-(tetrazol-5-yl)-aniline;
4-Amino-N-methyl-3-(1H-tetrazol-5-yl)-benzamide;
[4-Amino-3-(1H-tetrazol-5-yl)-benzoylamino]-acetic acid;
3-[4-Amino-3-(1H-tetrazol-5-yl)-phenyl]-acrylic acid methyl ester;
3-[4-Amino-3-(1H-tetrazol-5-yl)-phenyl]-propionic acid methyl ester;
N-[4-Amino-3-(1H-tetrazol-5-yl)-phenyl]-malonamic acid;
3-[4-Amino-3-(1H-tetrazol-5-yl)-phenyl]-N,N-dimethyl-acrylamide;
3-[4-amino-3-(1H-tetrazol-5-yl)-phenyl]-N-methyl-acrylamide;
4-Amino-N,N-diethyl-3-(1H-tetrazol-5-yl)-benzamide;
4-Amino-3-(1H-tetrazol-5-yl)-benzoyl-piperidin-1-yl;
4′-Amino-3′-(1H-tetrazol-5-yl)-biphenyl-4-carboxylic acid amide;
4-Amino-N,N-dimethyl-3-(1H-tetrazol-5-yl)-benzamide;
[4-Amino-N-methyl-3-(1H-tetrazol-5-yl)-benzoylamino]-acetic acid;
3-[4-Amino-3-(1H-tetrazol-5-yl)-phenyl]-N-methyl-propionamide;
N-[4-Amino-3-(1H-tetrazol-5-yl)-phenyl]-benzamide.

Example 18
N-(3,5-Bis-trifluoromethyl-phenyl)-N′-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4′-carboxylic acid dimethylamide] urea

2′-Amino-3′-(1H-tetrazol-5-yl)-biphenyl-4-carboxylic acid dimethylamide (1 g, 3.2 mmol) in toluene (25 ml) was added 3,5-bis-(trifluoromethyl)-phenyl isocyanate (0.88 g, 3.3 mmol, app 1 eq.) and triethylamine (0.36 g, 3.6 mmol, 1.2 eq.), the reaction mixture was stirred overnight, an oil in the bottom of the flask was isolated. The oil was dissolved in 2-propanol (20 ml), the solution was added hydrochloric acid (1M) until pH = 2-3, the title compound precipitated. Yield 0.86 g. M.p. 222-224°C.

The following compounds were made analogously:
N-(3-Chloro-4-fluoro-phenyl)-*N′*-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4′-sulfonic acid-dimethylamide] urea; Mp. 240-243°C;

N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N'*-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-sulfonic acid-dimethylamide] urea; Mp. 254-258°C;
N-(3-Fluoro-5-trifluoromethyl-phenyl)-N'-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-sulfonic acid-dimethylamide] urea; M.p. 255-256°C;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-sulfonic acid-dimethylamide] urea; M.p.203-205°C;
N-(3,5-Difluoro-phenyl)-N'-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-sulfonic acid-dimethylamide] urea; M.p. 254-255°C;
N-(3,5-Dichloro-phenyl)-N'-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-carboxylic acid dimethylamide] urea; M.p. 201-204°C;
N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[2-bromo-4-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 229-233°C;
N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[2,6-dibromo-3-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 220-222°C;
4-Chloro-2-(3-cyclohexyl-ureido)-benzoic acid; M.p.
N-Cyclohexyl-N'-(2,3-difluoro-4-trifluoromethyl-phenyl) urea;
[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
1-(3,5-Bis-trifluoromethyl-phenylcarbamoyl)-pyrroline-2-carboxylic acid;
1-(3,5-Bis-trifluoromethyl-phenylcarbamoyl)-4-hydroxy-pyrroline-2-carboxylic acid;
N-Cyclohexyl-N'-(2,3-difluoro-phenyl) urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[2-bromo-5-(1H-tetrazol-5-yl)-phenyl] urea;
N-(Cyclohexyl)-N'-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
5-Bromo-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]-benzoic acid;
2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-cyclohexanecarboxylic acid;
[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-(5-trifluoromethyl-phenyl)-acetic acid;
5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3-bromo-phenyl)-ureido]-benzoic acid;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
[3-(4-Chloro-3-fluoro-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
N-(3-Bromo-phenyl)-N'-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-N'-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3-Chloro-phenyl)-N'-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
[3-(3,5-Dichloro-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]-benzoic acid;
N-(3,5-Bis-trifluormethyl-phenyl)-N'-(phenyl-2-boronic acid) urea;
N-(4-Chloro-3-fluoro-phenyl)-N'-(phenyl-2-boronic acid) urea;
N-(3,5-Dichloro-phenyl)-N'-(phenyl-2-boronic acid) urea;

N-Cyclohexyl-N´-(phenyl-2-boronic acid) urea;
N-(2,6-Dichlooro-pyridin-4-yl)-N´-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 201-203°C;
N-Cyclohexyl-N´-[4´-(N´´,N´´-dimethyl-1-carbonyl)-2-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea; M.p. 156-158°C;
N-(2,6-Dichloro-pyridin-4-yl)-N´-[4´-(N´´,N´´-dimethyl-1-carbonyl)-2-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea; M.p. 163.8-164.5°C;
N-Cyclohexyl-N´-[4-bromo-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 233-239°C;
N-(2,6-Dichloro-pyridin-4-yl)-N´-[4-bromo-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 231-233°C;
5-Chloro-2-[3-(pyridin-3-yl)-ureido]-benzoic acid; M.p. > 240°C;
5-Bromo-2-[3-(pyridin-3-yl)-ureido]-benzoic acid; M.p. > 240°C;
3,5-Dichloro-2-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid; M.p. 259-261°C;
3,5-Dichloro-2-[3-(3-chloro-4-fluoro-phenyl)-ureido]-benzoic acid; M.p.174.5-175.9°C;
3,5-Dichloro-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]-benzoic acid; M.p.199-200°C;
3,5-Dichloro-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzoic acid; M.p.190.3-191.1°C;
3,5-Dichloro-2-[3-(4-fluoro-3-trifluoromethyl-phenyl)-ureido]-benzoic acid; M.p. 180-181°C;
3,5-Dichloro-2-[3-(3-fluoro-5-trifluoromethyl-phenyl)-ureido]-benzoic acid; M.p. 168-169°C;
3,5-Dichloro-2-[3-(3,5-difluoro-phenyl)-ureido]-benzoic acid; M.p. 245-249°C;
N-(4-Fluoro-3-trifluoromethyl-phenyl)-N´-[2,4-dibromo-6-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 195-196°C;
N-(3,4-Dichloro-phenyl)-N´-[2,4-dibromo-6-(1H-tetrazol-5-yl)-phenyl] urea; 201-203°C;
2-[3-(Thiophen-2-yl)-ureido]-benzoic acid;
2-[3-(Pyridin-4-yl)-ureido]-benzoic acid; M.p.> 230°C;
4-Chloro-2-[3-(pyridin-4-yl)-ureido]-benzoic acid; M.p. > 270°C;
5-Bromo-2-[3-(pyridin-4-yl)-ureido]-benzoic acid;
2-[3-(Pyridin-3-yl)-ureido]-nicotinic acid; M.p. > 220°C;
1-(4-Chloro-3-trifluoromethyl-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid; M.p. 159-161°C;
1-(3-Chloro-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid; M.p. 157-158°C;
1-(3-Bromo-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid; M.p. 176-177°C;
1-(3,5-Dichloro-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid; M.p. 180-181°C;
1-(Cyclohexyl-carbamoyl)-pyrrolidine-2-carboxylic acid; M.p 172-174°C;
1-(2,6-Dichloro-pyridin-4-ylcarbamoyl)-pyrrolidine-2-carboxylic acid; M.p. 177-178°C;
2-[(3-(3-Chloro-phenyl)-ureido]-cyclohexanecarboxylic acid; M.p. 194-195°C;
2-[(3-(3-Bromo-phenyl)-ureido]-cyclohexanecarboxylic acid; M.p 199-200°C;

2-[3-(3,5-Dichloro-phenyl)-ureido]-cyclohexanecarboxylic acid; M.p. 141-142°C;
2-(3-Cyclohexyl-ureido)-cyclohexanecarboxylic acid; M.p. 190-191°C;
2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-cyclohexane carboxylic acid; M.p. 199-200°C;
4-Chloro-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]-benzoic acid; M.p. 200-201°C;
5-Bromo-2-[3-(3-chloro-phenyl)-ureido]-benzoic acid; M.p. 194-195°C;
2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-nicotinic acid;
N-(2,3-Difluoro-4-trifluoromethyl-phenyl)-N′-(pyridin-3-yl) urea; M.p. 232-235°C;
N-[5-Chloro-2-(1H-tetrazol-5-yl)-phenyl]-N′-(pyridin-3-yl) urea; M.p. 214-220°C;
N-(Pyridin-3-yl)-N′-(2,3-difluoro-phenyl) urea; M.p. 211-215°C;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N′-(2,3-difluoro-4-trifluoromethyl-phenyl) urea; M.p. 194-195°C;
N-(2,6-Dichloro-pyridin-4-yl)-N′-(2,3-difluoro-4-trifluoromethyl-phenyl) urea; M.p. 210-211°C;
N-[4-Bromo-2-(1H-tetrazol-5-yl)-phenyl]-N′-(pyridin-3-yl) urea; M.p. 193-194°C;
2-[3-(Pyridin-3-yl)-ureido]-phenyl-boronic acid; M.p. 220-227°C;
5-Bromo-2-(3-cyclohexyl-ureido)-benzoic acid; M.p. 178-179°C;
[3-(3-Chloro-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid; M.p. 153-187°C;
N-(2,3-Difluoro-4-trifluoromehyl-phenyl)-N′-(pyridin-4-yl) urea; M.p. 205-206°C;
N-(2,3-Difluoro-phenyl)-N′-(pyridin-4-yl) urea; M.p. 201-215°C;
2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-phenyl-boronic acid; M.p. 232-233°C;
2-[3-(3-Bromo-phenyl)-ureido]-phenyl-dihydroxy-borane; M.p. 226-227°C;
2-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-cyclohexanecarboxylic acid; M.p. 213-214°C;
2-[3-(3-Chloro-phenyl)-ureido]-cyclohexanecarboxylic acid; M.p. 173-178°C;
2-[3-(3-Bromo-phenyl)-ureido]-cyclohexanecarboxylic acid; M.p. 175-223°C;
2-[3-(2,6-Dichloro-phenyl)-ureido]-cyclohexanecarboxylic acid; M.p. 182-241°C;
1-(4-Chloro-3-trifluoromethyl-phenylcarbamoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid; M.p. 67-80°C;
1-(3-Chloro-phenylcarbamoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid; M.p. 156-157°C;
1-(3-Bromo-phenylcarbamoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid;
1-(Pyridin-3-ylcarbamoyl)-pyrrolidine-2-carboxylic acid; M.p. 185-186°C;
2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-cyclohexanecarboxylic acid; M.p. 168-197°C;
4-Chloro-2-[3-(thiazol-2-yl)-ureido]-benzoic acid methyl ester;
5-Bromo-2-[3-(pyridin-2-yl)-ureido]-benzoic acid methyl ester;
4-Chloro-2-[3-(5-chloro-pyridin-2-yl)-ureido]benzoic acid;
5-Bromo-2-(3-thiazol-2-yl-ureido)-benzoic acid methyl ester;
2-[3-(5-Bromo-pyridin-3-yl)-ureido]-4-chloro-benzoic acid; M.p. >220°C;
5-Bromo-2-[3-(pyridin-2-yl)-ureido]-benzoic acid;

{2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid;
N-(3-Methoxy-phenyl)-N′-[4′-(N′′,N′′-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(2-Methoxy-phenyl)-N′-[4′-(N′′,N′′-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(4-Methoxy-phenyl)-N′-[4′-(N′′,N′′-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(Naphthalen-1-yl)-N′-[4′-(N′′,N′′-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(2-Trifluoromethyl-phenyl)-N′-[4′-(N′′,N′′-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N′-[4′-(N′′,N′′-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-[2,4-Dibromo-6-(1H-tetrazol-5-yl)-phenyl]-N′-(2,6-dichloro-pyridin-4-yl) urea; M.p. 202-203°C;
N-(3,5-Dichloro-phenyl)-N′-[2,4-dibromo-6-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 221-223°C;
3-Bromo-2-[3-(2H-1λ^4-thiazol-2-yl)-ureido]-benzoic acid; M.p. >250°C;
{2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester; M.p. 90-197°C;
{2-[3-(3-chloro-phenyl)-ureido]-phenyl}-phosphonic acid diethyl ester; M.p. oil;
{2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester; M.p. oil;
{2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester; M.p. 156-158°C;
{5-Bromo-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester; M.p. 152-158°C;
{5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester; M.p. oil;
{5-Bromo-2-[3-(3-chloro-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester; M.p. 160-207°C;
{5-Bromo-2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester; M.p.145-250°C;
{5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester; M.p. 139-144°C;
{5-Bromo-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]phenyl}-phosphonic acid diethyl ester;
2-{[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester; M.p. 205-206°C;

2-{[3-(3,5-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester; M.p. 195-196°C;
2-[(3-Phenyl-ureido)-benzyl]-phsophonic acid dimethyl ester;
2-[3-(4-Chloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester; M.p. 200-202°C;
2-{[3-(3,4-Dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester; M.p. 197-198°C;
{5-Chloro-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester; M.p. 210-211°C;
{5-Chloro-2-[3-(3,5-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester; M.p. 201-205°C;
[5-Chloro-2-(3-phenyl-ureido)-benzyl]-phosphonic acid dimethyl ester; M.p. 193-197°C;
{5-Chloro-2-[3-(3,4-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
{5-Chloro-2-[3-(3,4-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester; M.p. 208-212°C;
2,5-Dichloro-3-[3-(3-bromo-phenyl)-ureido]-benzoic acid; M.p. 254-255°C;
2,5-Dichloro-3-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid; M.p. 256-257°C;
{2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-phenyl}-phosphonic acid diethyl ester; M.p. 166-167°C;
{2-[3-(2-Trifluoromethyl-phenyl)-ureido]-phenyl}-phosphonic acid diethyl ester; M.p. oil;
5-Chloro-2-[3-(1H-indol-2-yl)-ureido]-benzoic acid; M.p. > 200°C;
5-Bromo-2-[3-(1H-indol-2-yl)-ureido]-benzoic acid; M.p > 230°C;
3-[3-(3-Bromo-phenyl)-ureido]-5-trifluoro-benzoic acid; M.p. 230-231°C;
3-[3-(3,5-Dichloro-phenyl)-ureido]-5-trifluoro-benzoic acid; M.p. 218-233°C;
3-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-biphenyl-4-carboxylic acid amide; M.p. 210-211°C;
3-[3-(3,5-Dichloro-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
3-[3-(2,3-Dichloro-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
3-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
4-[3-(3,5-Dichloro-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-[3-(3,5-Difluoro-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-[3-(2-Chloro-phenyl)-ureido]-biphenyl-3-carboxylic acid;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N′-[4′-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(3,5-Dichloro-phenyl)-N′-[4′-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N′-[4′-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;

N-(3,5-Difluoro-phenyl)-N´-[4´-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(2-Chloro-phenyl)-N´-[4´-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
4-Chloro-2-[3-(5-phenyl-2H-pyrazol-3-yl)-ureido]-benzoic acid; M.p > 270°C;
2-[3-(2-chloro-pyridin-3-yl)-ureido]-nicotinic acid; M.p. > 260°C;
4-Chloro-2-[3-(2-chloro-pyridin-3-yl)-ureido]-benzoic acid; M.p. > 215°C;
2-[3-(4-Chloro-phenyl)-ureido]-5-iodo-benzoic acid; M.p. > 200 °C;
5-Chloro-2-[3-(5-oxo-1-phenyl-pyrrolidin-3-yl)-ureido]-benzoic acid; M.p. > 240°C;
5-Bromo-2-(3-phenyl-ureido)-benzoic acid; M.p. > 200°C;
5-Bromo-2-[3-(2-fluoro-phenyl)-ureido]-benzoic acid; M.p. > 200°C;
5-Bromo-2-[3-(2-chloro-phenyl)-ureido]-benzoic acid; M.p. > 220°C;
5-Bromo-2-[3-(3,5-dimethyl-phenyl)-ureido]-benzoic acid; M.p. > 210°C;
5-Bromo-2-[3-(3,5-difluoro-phenyl)-ureido]-benzoic acid; M.p. 214-215°C;
5-Bromo-2-[3-(3,5-dimethoxy-phenyl)-ureido]-benzoic acid; M.p. 194-195°C;
N-(3,5-Dichloro-phenyl)-N´-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N´-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 205-207°C;
N-(3,5-Difluoro-phenyl)-N´-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 212-214°C;
5-Bromo-2-[3-(2,6-dichloro-phenyl)-ureido]-benzoic acid; M.p. > 225°C;
5-Bromo-2-[3-(2-bromo-phenyl)-ureido]-benzoic acid; M.p. > 225°C;
5-Bromo-2-[3-(4-chloro-3-nitro-phenyl)-ureido]-benzoic acid; M.p. > 230°C;
5-Bromo-2-[3-(4-butoxy-phenyl)-ureido]-benzoic acid; M.p. > 195°C;
5-Chloro-2-[3-(2-chloro-phenyl)-ureido]-benzoic acid; M.p. > 210°C;
5-Chloro-2-[3-(3,5-dimethyl-phenyl)-ureido]-benzoic acid; M.p. > 200°C;
2-[3-(4-Biphenyl)-ureido]-5-bromo-benzoic acid; M.p. > 200°C;
5-Chloro-2-[3-(3-iodo-phenyl)-ureido]- -benzoic acid; M.p. > 210°C;
5-Chloro-2-(3-phenyl-ureido)-benzoic acid; M.p. > 195°C;
5-Chloro-2-[3-(2-fluoro-phenyl)-ureido]-benzoic acid; M.p. > 195°C;
N-(3,5-Bis-trifluoromethyl)-N´-[2,4-dichloro-5-(1H-tetrazol-5yl)-phenyl] urea; M.p. > 200-203°C;
5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-nicotinic acid; M.p. > 300°C;
N-(3,5-Dichloro-phenyl)-N´-[4-(N´´-methyl-carboxamide)- 2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 276-277°C;
N-(3,5-Difluoro-phenyl)-N´-[4-(N´´-methyl-carboxamide)- 2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 277-278°C;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N´-[4-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 187-191°C;

N-(4-Chloro-3-trifluoromethyl-phenyl)-N´-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 244-248°C;
N-(3,5-Dichloro-phenyl)-N´-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 237-245°C;
N-(3,5-Bis-trifluoromethyl-phenyl)-N´-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-N´-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 257-258°C;
N-(2-Chloro-phenyl)-N´-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 184-185°C;
N-(4-Chloro-3-trifluoro-phenyl)-N´-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 168-169°C;
N-(3,5-Dichloro-phenyl)-N´-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 169-177°C;
N-(3,5-Bis-trifluoromethyl-phenyl)-N´-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 194-195°C;
N-(3,5-Difluoro-phenyl)-N´-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 173-177°C;
N-(2-Chloro-phenyl)-N´-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 228-229°C;
5-Bromo-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]-nicotinic acid; M.p. > 300°C;
N-(3,5-Dichloro-phenyl)-N´-[4-(N´´-malonamic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 223-225°C;
N-(3,5-Bis-trifluoromethyl-phenyl)-N´-[4-(N-malonamic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 172-175°C;
N-(3,5-Difluoro-phenyl)-N´-[4-(N´´-malonamic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 170-173°C;
N-(2-Chloro-phenyl)-N´-[4-(N´´-malonamic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 158-160°C;
N-(3,5-Bis-trifluoromethyl-phenyl)-N´-{4-[(N´´,N´´-dimethyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl} urea;
N-(3,5-Difluoro-phenyl)-N´-{4-[(N´´,N´´-dimethyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl} urea;
N-(2-Chloro-phenyl)-N´-{4-[(N´´,N´´-dimethyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl} urea;
N-(3,5-Dichloro-phenyl)-N´-{4-[(N´´-methyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl} urea;
N-(3,5-Difluoro-phenyl)-N´-{4-[(N´´-methyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl} urea;

N-(2-Chloro-phenyl)-N′-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-N′-[4-(N′′,N′′-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N′-[4-(N′′,N′′-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-N′-[4-(N′′,N′′-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(2-Chloro-phenyl)-N′-[4-(N′′,N′′-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 174-177°C;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N′-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 210-212°C;
N-(3,5-dichloro-phenyl)-N′-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 192-196°C;
N-(3,5-Bis-trifluoromethyl-phenyl)-N′-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 189-190°C;
N-(3,5-Difluoro-phenyl)-N′-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 183-185°C;
N-(3,5-Dichloro-phenyl)-N′-[4′-(carbonyl-(N′′-methyl)amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea; M.p. 286-287°C;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N′-[4′-carboxamide-2-(1H-tetrazol-5-yl)-4-biphenyl] urea; M.p. 245-247°C;
N-(3,5-Dichloro-phenyl)-N′-[4′-carboxamide-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N′-[4′-carboxamide-2-(1H-tetrazol-5-yl)-4-biphenyl] urea; M.p. 190-244°C;
N-(3,5-Difluoro-phenyl)-N′-[4′-carboxamide-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Dichloro-phenyl)-N′-[4-(N′′,N′′-dimethyl-caboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 184-244°C;
N-(3,5-Difluoro-phenyl)-N′-[4-(N′′,N′′-dimethyl-caboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 183-198°C;
N-(4-Chloro-3-trifluoromethyl)-N′-[4-(N′′,N′′-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p.191-240°C;
N-(3,5-Dichloro-phenyl)-N′-[4′-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea; M.p. 265-266°C;
N-(3,5-Difluoro-phenyl)-N′-[4′-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea; M.p. 235-242°C;
N-(2-Chloro-phenyl)-N′-[4′-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea; M.p. 253-254°C;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N′-{4′-[carbonyl-(N′′-methyl)-amino-acetic acid]-2-(1H-tetrazol-5-yl)-4-biphenyl} urea; M.p. 249-250°C;

N-(3,5-Dichloro-phenyl)-N′-{4′-[carbonyl-(N′′-methyl)-amino-acetic acid]-2-(1H-tetrazol-5-yl)-4-biphenyl} urea; M.p. 251-286°C;
N-(3,5-Bis-trifluoromethyl-phenyl)-N′-{4′-[carbonyl-(N′′-methyl)-amino-acetic acid]-2-(1H-tetrazol-5-yl)-4-biphenyl} urea; M.p. 190-191°C;
N-(3,5-Difluoro-phenyl)-N′-[4′-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea; M.p. decomp.;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N′-[4-(N′′-methyl-propylamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-N′-[4-(N′′-methyl-propyamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluromethyl-phenyl)-N′-[4-(N′′-methyl-propylamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-N′-[4-(N′′-methyl-propylamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(2-chloro-phenyl)-N′-[4-(N′′-methyl-propylamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
5-Chloro-2-[3-(3,5-difluoro-phenyl)-ureido]-benzoic acid;
5-Chloro-2-[3-(3,5-dimethoxy-phenyl)-ureido]-benzoic acid;
5-Chloro-2-[3,4-dichloro-phenyl)-ureido]-benzoic acid;
2-[3-(4-Butoxy-phenyl)-ureido]-5-chloro- benzoic acid;
5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]-nicotinic acid; M.p > 300°C;
5-Bromo-2-[3-(3,5-difluoro-phenyl)-ureido]-nicotinic acid; M.p > 300°C;
N-(2,6-Dichloro-phenyl)-N′-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 214-215°C;
N-(2,4,6-trichloro-phenyl)-N′-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 207-209°C;
5-Bromo-2-[3-(2,4,6-trichloro-phenyl)-ureido]-nicotinic acid; M.p. > 300°C;
N-(3,5-Dichloro-phenyl)-N′-[4-benzamide-2-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 238-239°C;
N-(3,5-Difluoro-phenyl)-N′-[4-benzamide-2-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 254-256°C;
N-(3,5-Bis-trifluoromethyl-phenyl)-N′-[4-benzamide-2-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 250-253°C;
N-(4-Chloro-3-trifluoromethyl-phenyl)- N′-[4-benzamide-2-(1H-tetrazol-5-yl)-phenyl) urea; M.p. 248-250°C;
5-Chloro-2-[3-(2,6-dichloro-phenyl)-ureido]-benzoic acid. M.p. > 300°C;
N-(3,5-Bis-trifluoromethyl-phenyl)-N′-[4′-(N′′-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea; M.p. 244-245°C;
N-(4-Chloro-3-trifluoromethyl-phenyl)- N′-[4-(N′′,N′′-dimethyl acryl-amide)-2-(1-H-tetrazol-5-yl)-phenyl] urea; M.p. 169-171°C;

N-(3,5-dichloro-phenyl)-N'-[4-(N'',N''-dimethyl acryl-amide)-2-(1-H-tetrazol-5-yl)phenyl] urea; M.p. 190-193°C;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4'-(N''-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea; M.p. 275-296°C;

Example 19
3,5-Bis-[3-(3-bromo-phenyl)-ureido]- benzoic acid

3,5-Diaminobenzoic acid (152 mg, 1 mmol) in anhydrous acetonitrile (5 ml) under an argon atmosphere was added 3-bromophenyl isocyanate (396 mg, 2 mmol, 2 eq.). The reaction mixture was stirred at 60 °C for 16 hours. The title compound precipitated out of solution and was isolated by filtration. Yield 377 mg. M.p. > 300°C.

The following compounds were made analogously:
3,5-Bis-[3-(3,5-dichloro-phenyl)-ureido]- benzoic acid; M.p. > 300°C;
3,5-Bis-[3-(3,5-difluro-phenyl)-ureido]- benzoic acid; M.p. > 300°C;
3,5-Bis-[3-(3,5-bis-trifluoromethylphenyl)-ureido]- benzoic acid; M.p. > 300°C.

Example 20
{2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid

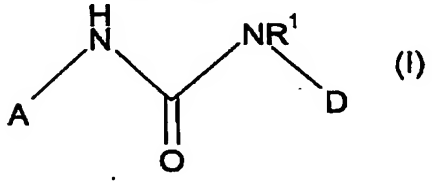
{2-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-phenyl}-phosphonic acid diethyl ester (400 mg, 0.8 mmol) was dissolved in anhydrous dichloromethane (3 ml). Under a argon atmosphere was added trimethylsilyl bromide (2 ml, 15 mmol, 19 eq.), the reaction mixture was heated at reflux overnight then evaporated to dryness, to the residue was added water (10 ml) and ethyl acetate (10 ml), the organic layer was separated, dried and evaporated. The title compound was crystallized from dichloromethane. Yield 340 mg, M.p. 153-157°C.

The following compounds were made analogously:
{2-[3-(3-chloro-phenyl)-ureido]phenyl}-phosphonic acid; M.p. 147-149°C;
{2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid; M.p. 145-151°C;
{2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid; M.p. 167-170°C;
{5-Bromo-2-[3-(3,5 bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid; M.p. 150-153°C;
{5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid; M.p. 267-273°C;
{5-Bromo-2-[3-(3-chloro-phenyl)-ureido]phenyl}-phosphonic acid; M.p. 160-207°C;
{5-Bromo-2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid; M.p. 204-210°C;

{5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid; M.p. 212-288°C;
{5-Bromo-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]phenyl}-phosphonic acid;
2-{[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid; M.p. 185-197°C;
2-{[3-(3,5-Dichloro-phenyl)-ureido]-benzyl}-phosphonic acid; M.p. 192-193°C;
2-[(3-Phenyl-ureido)-benzyl]-phsophonic acid; M.p. 166-168°C;
2-[3-(4-Chloro-phenyl)-ureido]-benzyl}-phosphonic acid; M.p. 184-191°C;
2-{[3-(3,4-Dichloro-phenyl)-ureido]-benzyl}-phosphonic acid; M.p. 177-178°C;
{5-Chloro-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid; M.p. 177-180°C;
{5-Chloro-2-[3-(3,5-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid; Mp. 181-182°C;
[5-Chloro-2-(3-phenyl-ureido)-benzyl]-phosphonic acid; M.p. 174-182°C;
{5-Chloro-2-[3-(4-chloro-phenyl)-ureido]-benzyl}-phosphonic acid; M.p. 189-190°C;
{5-Chloro-2-[3-(3,4-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid; M.p. 191-192°C;
{2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-phenyl}-phosphonic acid; M.p. 185-189°C;
{2-[3-(2-Trifluoromethyl-phenyl)-ureido]-phenyl}-phosphonic acid; M.p. 155-162°C.

CLAIMS:

1. A chemical compound represented by general formula (I)

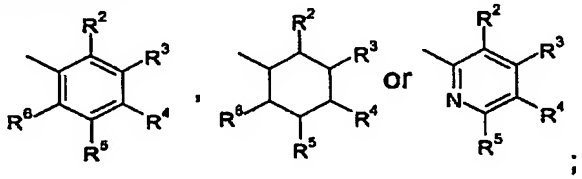


(I)

or a pharmaceutically acceptable salt thereof, wherein

A represents a ring system selected from the group consisting of:
cyclohexanyl, phenyl, pyridyl, thienyl, thiazolyl, naphthyl, indolyl, pyrazolyl and oxo-pyrrolidinyl;
which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:
halogen, trifluoromethyl, nitro, alkyl, alkoxy, and phenyl; and

R^1 represents -H; and
D represents



;

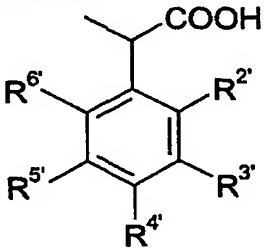
wherein
one of R^2, R^3, and R^4 is selected from the group consisting of:
tetrazolyl, $-COOR^a$, $-B(OH)_2$, $-PO(OR^a)_2$, $-CH_2-PO(OR^a)_2$, and -CONH;
wherein R^a is hydrogen or alkyl;
or R^2 and R^3 or R^3 and R^4 both represent fluoro; and
R^5, R^6 and the remaining one or two of R^2, R^3 and R^4 independently of each other represent:

- hydrogen, halogen, trifluoromethyl,
- $-CH=CH-COOR^b$, $-CH_2-CH_2-COOR^b$,
- $-CO-NR^b-CH_2-COOR^c$; $-CO-NR^bR^c$,
- $-CH=CH-CO-NR^bR^c$; $-CH_2-CH_2-CO-NR^bR^c$,
- piperidylcarbonyl,
- $-NH-CO-R^d$ or $-NH-CO-NH-R^d$;
  wherein R^d is phenyl optionally substituted with one or more substituents independently selected from halogen or trifluoromethyl; or

- phenyl optionally substituted with
  $-SO_2-NR^bR^c$, $-CO-NR^bR^c$, $-CO-NR^b-CH_2-COOR^c$, or piperidylcarbonyl;

wherein R^b and R^c independently are hydrogen or alkyl;

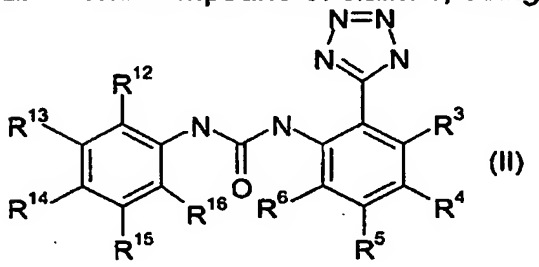
or R^1 represents -H; and
D represents



wherein $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, $R^{6'}$ independently of each other represent hydrogen, halogen, or trifluoromethyl:

or R^1 together with D forms $-CHR^e-CH_2-CHR^f-CH_2-$;
wherein R^e represents -COOH;
R^f represents hydrogen or hydroxy.

2. The compound of claim 1, being a compound of general formula (II)



(II)

or a pharmaceutically acceptable salt thereof, wherein

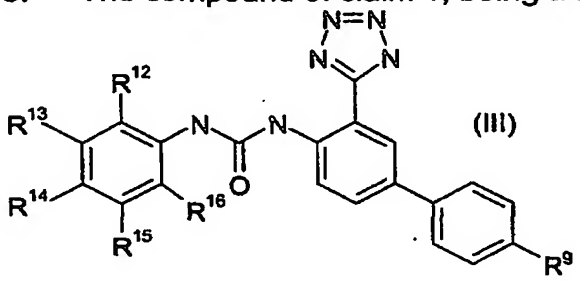
R^3, R^4, R^5 and R^6 independently of each other represent:

- hydrogen, halogen, trifluoromethyl,
- $-CH=CH-COOR^b$, $-CH_2-CH_2-COOR^b$,
- $-CO-NR^b-CH_2-COOR^c$; $-CO-NR^bR^c$,
- $-CH=CH-CO-NR^bR^c$; $-CH_2-CH_2-CO-NR^bR^c$,
- piperidylcarbonyl,
- $-NH-CO-R^d$ or $-NH-CO-NH-R^d$;
  wherein R^d is phenyl optionally substituted with one or more substituents independently selected from halogen or trifluoromethyl (bromo, dichloro); or
- phenyl optionally substituted with

$-SO_2-NR^bR^c$, $-CO-NR^bR^c$, $-CO-NR^b-CH_2-COOR^c$, or piperidylcarbonyl;
wherein R^b and R^c independently are hydrogen or alkyl;

R^{12}, R^{13}, R^{14}, R^{15}, and R^6 independently of each other represent
hydrogen, halogen, trifluoromethyl, nitro, alkyl, or alkoxy.

3. The compound of claim 1, being a compound of general formula (III)



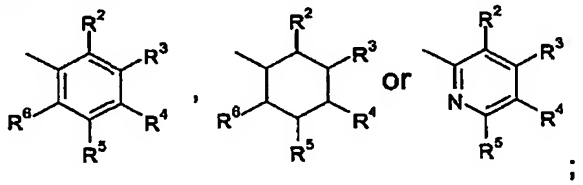
(III)

or a pharmaceutically acceptable salt thereof, wherein

R^9 represents $-CO-NR^bR^c$, $-CO-NR^b-CH_2-COOR^c$, or piperidylcarbonyl;
wherein R^b and R^c independently are hydrogen or alkyl;

two of R^{12}, R^{13}, R^{14}, R^{15}, and R^{16} independently of each other represent
halogen, trifluoromethyl, nitro, alkyl, or alkoxy;
and the remaining three of R^{12}, R^{13}, R^{14}, R^{15}, and R^{16} represent hydrogen.

4. The formula of claim 1, wherein
A represents a ring system selected from the group consisting of:
cyclohexanyl, phenyl, pyridyl, thienyl, thiazolyl, and pyrazolyl;
which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:
halogen, trifluoromethyl, nitro, alkyl, alkoxy, and phenyl; and
R^1 represents -H; and
D represents



;

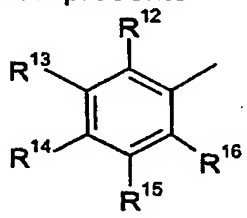
wherein
R^2 represents $-COOR^a$;
wherein R^a is hydrogen or alkyl;
R^3, R^4, R^5, and R^6 independently of each other represent:

- hydrogen, halogen, trifluoromethyl,
- -NH-CO-R^d or -NH-CO-NH-R^d;
  wherein R^d is phenyl optionally substituted with one or more substituents independently selected from halogen or trifluoromethyl; or
- phenyl optionally substituted with
  $-SO_2-NR^bR^c$, $-CO-NR^bR^c$, $-CO-NR^b-CH_2-COOR^c$, or piperidylcarbonyl;

wherein R^b and R^c independently are hydrogen or alkyl.

5. The compound of claim 4, wherein

A represents



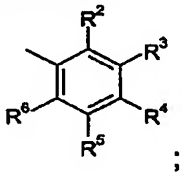
wherein R^{12}, R^{13}, R^{14}, R^{15}, and R^{16} independently of each other represent:
halogen, trifluoromethyl, nitro, alkyl, alkoxy, or phenyl.

6. The compound of claim 1, wherein

A represents a ring system selected from the group consisting of:
cyclohexanyl, phenyl, and pyridyl;
which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:
halogen, trifluoromethyl, nitro, alkyl, and alkoxy; and

R^1 represents -H; and

D represents



;

wherein

R^2 represents $-B(OH)_2$, $-PO(OR^a)_2$, $-CH_2-PO(OR^a)_2$, or -CONH;
wherein R^a is hydrogen or alkyl (hydrogen, methyl, ethyl);
R^2, R^3, R^4, R^5, and R^6 independently of each other represent:
hydrogen, halogen, trifluoromethyl, or phenyl.

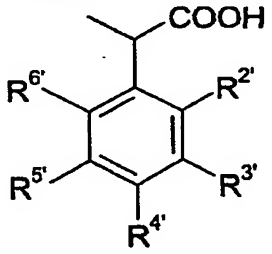
7. The compound of claim 1, wherein

A represents phenyl optionally substituted with one or more substituents independently selected from the group consisting of:

halogen, trifluoromethyl, nitro, alkyl, and alkoxy; and

R^1 represents -H; and

D represents



wherein $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, $R^{6'}$ independently of each other represent hydrogen, halogen, or trifluoromethyl.

8. The compound of claim 1, wherein

A represents a ring system selected from the group consisting of:

cyclohexanyl, phenyl, and pyridyl;

which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:

halogen, trifluoromethyl, nitro, alkyl, and alkoxy; and

R^1 together with D forms $-CHR^e-CH_2-CHR^f-CH_2-$;

wherein R^e represents -COOH;

R^f represents hydrogen or hydroxy.

9. The compound of claim 1, wherein

A represents a ring system selected from the group consisting of:

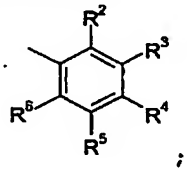
cyclohexanyl, phenyl, and pyridyl;

which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:

halogen, trifluoromethyl, nitro, alkyl, and alkoxy;

R^1 represents -H; and

D represents



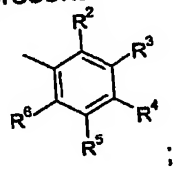
;

wherein

R^2 and R^3 or R^3 and R^4 both represent fluoro; and
R^5, R^6 and the remaining one or two of R^2, R^3 and R^4 independently of each other represent hydrogen, halogen, or trifluoromethyl.

10. The compound of claim 1, wherein
A represents a ring system selected from the group consisting of:
cyclohexanyl, pyridyl, and naphthyl;
which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:
halogen, trifluoromethyl, nitro, alkyl, and alkoxy; and

R^1 represents -H; and
D represents



;

wherein
R^2 represents tetrazolyl;
R^3, R^4, R^5, and R^6 independently of each other represent:
- hydrogen, halogen, trifluoromethyl; or
- phenyl substituted with
$-SO_2-NR^bR^c$, $-CO-NR^bR^c$, $-CO-NR^b-CH_2-COOR^c$, or piperidylcarbonyl;
wherein R^b and R^c independently are hydrogen or alkyl (methyl).

11. The compound of claim 1, being
N-(3,5-Bis-trifluoromethyl-phenyl)-N′-[2-bromo-4-(1H-tetrazol-5-yl)-phenyl urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N′-[2,6-dibromo-3-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N′-[2-bromo-5-(1H-tetrazol-5-yl)-phenyl] urea;
5-Chloro-2-[3-(1H-indol-2-yl)-ureido]-benzoic acid;
5-Bromo-2-[3-(1H-indol-2-yl)-ureido]-benzoic acid;
N-(3-Fluoro-5-trifluoromethyl-phenyl)-N′-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4′-sulfonic acid-dimethylamide] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N′-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4′-sulfonic acid-dimethylamide] urea;
N-(3,5-Difluoro-phenyl)-N′-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4′-sulfonic acid-dimethylamide] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N′-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;

N-(3,5-Bis-trifluoromethyl-phenyl)-N′-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3-Bromo-phenyl)-N′-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-N′-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3-Chloro-phenyl)-N′-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(4-Fluoro-3-trifluoromethyl-phenyl)-N′-[2,4-dibromo-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,4-Dichloro-phenyl)-N′-[2,4-dibromo-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3-Methoxy-phenyl)-N′-[4′-(N′′,N′′-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(2-Methoxy-phenyl)-N′-[4′-(N′′,N′′-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(4-Methoxy-phenyl)-N′-[4′-(N′′,N′′-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(2-Trifluoromethyl-phenyl)-N′-[4′-(N′′,N′′-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N′-[4′-(N′′,N′′-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(3,5-Dichloro-phenyl)-N′-[2,4-dibromo-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(2-Chloro-phenyl)-N′-[4′-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(3,5-Dichloro-phenyl)-N′-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N′-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-N′-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl)-N′-[2,4-dichloro-5-(1H-tetrazol-5yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-N′-[4-(N′′-methyl-carboxamide)- 2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-N′-[4-(N′′-methyl-carboxamide)- 2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N′-[4-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N′-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-N′-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N′-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-N′-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(2-Chloro-phenyl)-N′-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;

N-(4-Chloro-3-trifluoro-phenyl)-N´-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-N´-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N´-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-N´-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(2-Chloro-phenyl)-N´-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-N´-[4-(N´´-malonamic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N´-[4-(N-malonamic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-N´-[4-(N´´-malonamic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(2-Chloro-phenyl)-N´-[4-(N´´-malonamic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 158-160°C;
N-(3,5-Bis-trifluoromethyl-phenyl)-N´-{4-[(N´´,N´´-dimethyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl} urea;
N-(3,5-Difluoro-phenyl)-N´-{4-[(N´´,N´´-dimethyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl} urea;
N-(2-Chloro-phenyl)-N´-{4-[(N´´,N´´-dimethyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl} urea;
N-(3,5-Dichloro-phenyl)-N´-{4-[(N´´-methyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl} urea;
N-(3,5-Difluoro-phenyl)-N´-{4-[(N´´-methyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl} urea;
N-(2-Chloro-phenyl)-N´-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-N´-[4-(N´´,N´´-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N´-[4-(N´´,N´´-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-N´-[4-(N´´,N´´-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(2-Chloro-phenyl)-N´-[4-(N´´,N´´-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N´-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-dichloro-phenyl)-N´-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea;

N-(3,5-Bis-trifluoromethyl-phenyl)-N′-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-N′-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-N′-[4′-(carbonyl-(N′′-methyl)amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Dichloro-phenyl)-N′-[4-(N′′,N′′-dimethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-N′-[4-(N′′,N′′-dimethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(4-Chloro-3-trifluoromethyl)-N′-[4-(N′′,N′′-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(2-Chloro-phenyl)-N′-[4′-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N′-[4-(N′′-methyl-propylamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-N′-[4-(N′′-methyl-propyamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluromethyl-phenyl)-N′-[4-(N′′-methyl-propylamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-N′-[4-(N′′-methyl-propylamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(2-chloro-phenyl)-N′-[4-(N′′-methyl-propylamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(2,6-Dichloro-phenyl)-N′-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(2,4,6-trichloro-phenyl)-N′-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-N′-[4-benzamide-2-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-N′-[4-benzamide-2-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N′-[4-benzamide-2-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)- N′-[4-benzamide-2-(1H-tetrazol-5-yl)-phenyl) urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)- N′-[4-(N′′,N′′-dimethyl acryl-amide)-2-(1-H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-dichloro-phenyl)-N′-[4-(N′′,N′′-dimethyl acryl-amide)-2-(1-H-tetrazol-5-yl)phenyl] urea;
N-(3-Chloro-4-fluoro-phenyl)-*N*′-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4′-sulfonic acid-dimethylamide] urea;
N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N*′-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4′-sulfonic acid-dimethylamide] urea;

N-(3,5-Bis-trifluoromethyl-phenyl)-N´-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4´-carboxylic acid dimethylamide] urea
N-(3,5-Dichloro-phenyl)-N´-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4´-carboxylic acid dimethylamide] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N´-[4´-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(3,5-Dichloro-phenyl)-N´-[4´-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N´-[4´-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(3,5-Difluoro-phenyl)-N´-[4´-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N´-[4´-carboxamide-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Dichloro-phenyl)-N´-[4´-carboxamide-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N´-[4´-carboxamide-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Difluoro-phenyl)-N´-[4´-carboxamide-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Dichloro-phenyl)-N´-[4´-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Difluoro-phenyl)-N´-[4´-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N´-{4´-[carbonyl-(N´´-methyl)-amino-acetic acid]-2-(1H-tetrazol-5-yl)-4-biphenyl} urea;
N-(3,5-Dichloro-phenyl)-N´-{4´-[carbonyl-(N´´-methyl)-amino-acetic acid]-2-(1H-tetrazol-5-yl)-4-biphenyl} urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N´-{4´-[carbonyl-(N´´-methyl)-amino-acetic acid]-2-(1H-tetrazol-5-yl)-4-biphenyl} urea;
N-(3,5-Difluoro-phenyl)-N´-[4´-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea; M.p. decomp.;
N-(3,5-Bis-trifluoromethyl-phenyl)-N´-[4´-(N´´-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N´-[4´-(N´´-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
4-Chloro-2-(3-cyclohexyl-ureido)-benzoic acid;
5-Bromo-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]-benzoic acid;
2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-cyclohexanecarboxylic acid;
5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3-bromo-phenyl)-ureido]-benzoic acid;

5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]-benzoic acid;
N-(3,5-Bis-trifluormethyl-phenyl)-N´-(phenyl-2-boronic acid) urea;
N-(4-Chloro-3-fluoro-phenyl)-N´-(phenyl-2-boronic acid) urea;
N-(3,5-Dichloro-phenyl)-N´-(phenyl-2-boronic acid) urea;
N-Cyclohexyl-N´-(phenyl-2-boronic acid) urea;
5-Chloro-2-[3-(pyridin-3-yl)-ureido]-benzoic acid;
5-Bromo-2-[3-(pyridin-3-yl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(3-chloro-4-fluoro-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(4-fluoro-3-trifluoromethyl-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(3-fluoro-5-trifluoromethyl-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(3,5-difluoro-phenyl)-ureido]-benzoic acid;
2-[3-(Thiophen-2-yl)-ureido]-benzoic acid;
2-[3-(Pyridin-4-yl)-ureido]-benzoic acid;
4-Chloro-2-[3-(pyridin-4-yl)-ureido]-benzoic acid;
5-Bromo-2-[3-(pyridin-4-yl)-ureido]-benzoic acid;
2-[3-(Pyridin-3-yl)-ureido]-nicotinic acid;
2-[(3-(3-Chloro-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-[(3-(3-Bromo-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-[3-(3,5-Dichloro-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-(3-Cyclohexyl-ureido)-cyclohexanecarboxylic acid;
2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-cyclohexane carboxylic acid;
4-Chloro-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3-chloro-phenyl)-ureido]-benzoic acid;
2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-nicotinic acid;
5-Bromo-2-(3-cyclohexyl-ureido)-benzoic acid;
2-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-[3-(3-Chloro-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-[3-(3-Bromo-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-[3-(2,6-Dichloro-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-cyclohexanecarboxylic acid;
4-Chloro-2-[3-(thiazol-2-yl)-ureido]-benzoic acid methyl ester;
5-Bromo-2-[3-(pyridin-2-yl)-ureido]-benzoic acid methyl ester;
4-Chloro-2-[3-(5-chloro-pyridin-2-yl)-ureido]benzoic acid;
5-Bromo-2-(3-thiazol-2-yl-ureido)-benzoic acid methyl ester;
2-[3-(5-Bromo-pyridin-3-yl)-ureido]-4-chloro-benzoic acid;

5-Bromo-2-[3-(pyridin-2-yl)-ureido]-benzoic acid;
3-Bromo-2-[3-(2H-1λ^4-thiazol-2-yl)-ureido]-benzoic acid;
3-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
4-[3-(3,5-Dichloro-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-[3-(3,5-Difluoro-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-[3-(2-Chloro-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-Chloro-2-[3-(5-phenyl-2H-pyrazol-3-yl)-ureido]-benzoic acid;
2-[3-(2-chloro-pyridin-3-yl)-ureido]-nicotinic acid;
4-Chloro-2-[3-(2-chloro-pyridin-3-yl)-ureido]-benzoic acid;
2-[3-(4-Chloro-phenyl)-ureido]-5-iodo-benzoic acid;
5-Chloro-2-[3-(5-oxo-1-phenyl-pyrrolidin-3-yl)-ureido]-benzoic acid;
5-Bromo-2-(3-phenyl-ureido)-benzoic acid;
5-Bromo-2-[3-(2-fluoro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(2-chloro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3,5-dimethyl-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3,5-difluoro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3,5-dimethoxy-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(2,6-dichloro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(2-bromo-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(4-chloro-3-nitro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(4-butoxide-phenyl)-ureido]-benzoic acid;
5-Chloro-2-[3-(2-chloro-phenyl)-ureido]-benzoic acid;
5-Chloro-2-[3-(3,5-dimethyl-phenyl)-ureido]-benzoic acid;
2-[3-(4-Biphenyl)-ureido]-5-bromo-benzoic acid;
5-Chloro-2-[3-(3-iodo-phenyl)-ureido]- -benzoic acid;
5-Chloro-2-(3-phenyl-ureido)-benzoic acid;
5-Chloro-2-[3-(2-fluoro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-nicotinic acid;
5-Bromo-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]-nicotinic acid;
5-Chloro-2-[3-(3,5-difluoro-phenyl)-ureido]-benzoic acid;
5-Chloro-2-[3-(3,5-dimethoxy-phenyl)-ureido]-benzoic acid;
5-Chloro-2-[3,4-dichloro-phenyl)-ureido]-benzoic acid;
2-[3-(4-Butoxy-phenyl)-ureido]-5-chloro- benzoic acid;
5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]-nicotinic acid;
3,5-Bis-[3-(3,5-difluro-phenyl)-ureido]- benzoic acid;
5-Bromo-2-[3-(3,5-difluoro-phenyl)-ureido]-nicotinic acid;
5-Bromo-2-[3-(2,4,6-trichloro-phenyl)-ureido]-nicotinic acid;
5-Chloro-2-[3-(2,6-dichloro-phenyl)-ureido]-benzoic acid;

3,5-Bis-[3-(3,5-bis-trifluoromethylphenyl)-ureido]- benzoic acid;
2,5-Dichloro-3-[3-(3-bromo-phenyl)-ureido]-benzoic acid;
2,5-Dichloro-3-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid;
3,5-Bis-[3-(3-bromo-phenyl)-ureido]- benzoic acid
3,5-Bis-[3-(3,5-dichloro-phenyl)-ureido]- benzoic acid;
3-[3-(3-Bromo-phenyl)-ureido]-5-trifluoro-benzoic acid;
3-[3-(3,5-Dichloro-phenyl)-ureido]-5-trifluoro-benzoic acid;
3,5-Bis-[3-(3,5-bis-trifluoromethylphenyl)-ureido]- benzoic acid;
2-[3-(Pyridin-3-yl)-ureido]-phenyl-boronic acid;
2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-phenyl-boronic acid;
2-[3-(3-Bromo-phenyl)-ureido]-phenyl-dihydroxy-borane;
{2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid;
{2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid
{2-[3-(3-chloro-phenyl)-ureido]-phenyl}-phosphonic acid diethyl ester;
{2-[3-(3-chloro-phenyl)-ureido]phenyl}-phosphonic acid;
{2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid;
{2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid;
{5-Bromo-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{5-Bromo-2-[3-(3,5 bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid;
{5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid;
{5-Bromo-2-[3-(3-chloro-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{5-Bromo-2-[3-(3-chloro-phenyl)-ureido]phenyl}-phosphonic acid;
{5-Bromo-2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{5-Bromo-2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid;
{5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid;
{5-Bromo-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]phenyl}-phosphonic acid diethyl ester;
{5-Bromo-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]phenyl}-phosphonic acid;
2-{[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
2-{[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid;
2-{[3-(3,5-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;

2-{[3-(3,5-Dichloro-phenyl)-ureido]-benzyl}-phosphonic acid;
2-[(3-Phenyl-ureido)-benzyl]-phsophonic acid dimethyl ester;
2-[(3-Phenyl-ureido)-benzyl]-phsophonic acid;
2-[3-(4-Chloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
2-[3-(4-Chloro-phenyl)-ureido]-benzyl}-phosphonic acid;
2-{[3-(3,4-Dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
2-{[3-(3,4-Dichloro-phenyl)-ureido]-benzyl}-phosphonic acid;
{5-Chloro-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
{5-Chloro-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid;
{5-Chloro-2-[3-(3,5-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
{5-Chloro-2-[3-(3,5-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid;
[5-Chloro-2-(3-phenyl-ureido)-benzyl]-phosphonic acid dimethyl ester;
[5-Chloro-2-(3-phenyl-ureido)-benzyl]-phosphonic acid;
{5-Chloro-2-[3-(3,4-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
{5-Chloro-2-[3-(4-chloro-phenyl)-ureido]-benzyl}-phosphonic acid;
{5-Chloro-2-[3-(3,4-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
{5-Chloro-2-[3-(3,4-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid;
{2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-phenyl}-phosphonic acid diethyl ester;
{2-[3-(2-Trifluoromethyl-phenyl)-ureido]-phenyl}-phosphonic acid diethyl ester;
{2-[3-(2-Trifluoromethyl-phenyl)-ureido]-phenyl}-phosphonic acid;
3-[3-(3,5-Dichloro-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
3-[3-(2,3-Dichloro-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
3-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
{2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-phenyl}-phosphonic acid;
[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-(5-trifluoromethyl-phenyl)-acetic acid;
[3-(4-Chloro-3-fluoro-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
[3-(3,5-Dichloro-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
[3-(3-Chloro-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
1-(3,5-Bis-trifluoromethyl-phenylcarbamoyl)-pyrroline-2-carboxylic acid;
1-(3,5-Bis-trifluoromethyl-phenylcarbamoyl)-4-hydroxy-pyrroline-2-carboxylic acid;
1-(4-Chloro-3-trifluoromethyl-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid;
1-(3-Chloro-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid;
1-(3-Bromo-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid;
1-(3,5-Dichloro-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid;
1-(Cyclohexyl-carbamoyl)-pyrrolidine-2-carboxylic acid;
1-(2,6-Dichloro-pyridin-4-ylcarbamoyl)-pyrrolidine-2-carboxylic acid;
1-(4-Chloro-3-trifluoromethyl-phenylcarbamoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid;

1-(3-Chloro-phenylcarbamoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid;
1-(3-Bromo-phenylcarbamoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid;
1-(Pyridin-3-ylcarbamoyl)-pyrrolidine-2-carboxylic acid;
N-Cyclohexyl-N′-(2,3-difluoro-4-trifluoromethyl-phenyl) urea;
N-Cyclohexyl-N′-(2,3-difluoro-phenyl) urea;
N-(2,3-Difluoro-4-trifluoromethyl-phenyl)-N′-(pyridin-3-yl) urea;
N-(Pyridin-3-yl)-N′-(2,3-difluoro-phenyl) urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N′-(2,3-difluoro-4-trifluoromethyl-phenyl) urea;
N-(2,6-Dichloro-pyridin-4-yl)-N′-(2,3-difluoro-4-trifluoromethyl-phenyl) urea;
N-(2,3-Difluoro-4-trifluoromehyl-phenyl)-N′-(pyridin-4-yl) urea;
N-(2,3-Difluoro-phenyl)-N′-(pyridin-4-yl) urea;
N-(Cyclohexyl)-N′-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(2,6-Dichloro-pyridin-4-yl)-N′-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-Cyclohexyl-N′-[4′-(N′′,N′′-dimethyl-1-carbonyl)-2-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(2,6-Dichloro-pyridin-4-yl)-N′-[4′-(N′′,N′′-dimethyl-1-carbonyl)-2-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-Cyclohexyl-N′-[4-bromo-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(2,6-Dichloro-pyridin-4-yl)-N′-[4-bromo-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-[5-Chloro-2-(1H-tetrazol-5-yl)-phenyl]-N′-(pyridin-3-yl) urea;
N-[4-Bromo-2-(1H-tetrazol-5-yl)-phenyl]-N′-(pyridin-3-yl) urea;
N-(Naphthalen-1-yl)-N′-[4′-(N′′,N′′-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-[2,4-Dibromo-6-(1H-tetrazol-5-yl)-phenyl]-N′-(2,6-dichloro-pyridin-4-yl) urea;
or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of claims 1-11, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

13. The use of a compound according to any one of claims 1-11, or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to the blockade of chloride channels.

14. The use according to claim 13, wherein the disease, disorder or condition responsive to the blockade of chloride channels is a bone metabolic disease or an osteoclast related bone disease.

15. The use according to claim 13, wherein the disease, disorder or condition responsive to the blockade of chloride channels is osteoporosis, postmenopausal osteoporosis, secondary osteoporosis, osteolytic breast cancer bone metastasis, osteolytic cancer invation, Paget's disease of bone.

16. A method for the treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to responsive to the blockade of chloride channels, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a compound according to any one of the claims 1-11, or any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically acceptable salt thereof.

PATENT COOPERATION TREATY

PCT

REC'D 21 OCT 2004

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 224-204-WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/DK 03/00575	International filing date *(day/month/year)* 04.09.2003	Priority date *(day/month/year)* 05.09.2002
International Patent Classification (IPC) or both national classification and IPC C07C275/00		
Applicant NEUROSEARCH A/S		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23.02.2004	20.10.2004
Name and mailing address of the International preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Breimaier, W Telephone No. +49 89 2399-8327

Form PCT/IPEA/409 (Cover Sheet) (January 2004)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK 03/00575

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-47 as originally filed

Claims, Numbers

1-20 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 20

because:

☒ the said international application, or the said claims Nos. 20 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-20
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	1-19
	No:	Claims	20

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 20 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (art. 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

novelty

The subject-matter according to claims 1 to 20 is not novel in the sense of art. 33(2) PCT having regard to the following documents:

D1 : WO 02/39987, see compounds of general formula II which are chloride channel blockers (see in particular page 15, line 9 to page 17, line 2);
D2 : WO 98/47879, see compounds of general formula I (in particular the tetrazolyl substituted urea derivatives) which are chloride channel blockers (see pages 5 and 6 and the claims);
D3 : WO 00/24707, see compounds of the general formula on page 10, preferably the tetrazolyl substituted urea derivatives (see pages 11 to 13) which are chloride channel blockers (see page 9 and page 21, line 31 to page 22, line 9, examples and claims);
D4 : WO 97/45400, see the urea derivatives of the general formula according to claim 1 and the examples which are chloride channel blockers (see pages 5 and 15);
D5 : WO 02/064128, see claim 3, general formula (I) with R2=COOH ;
D6 : WO 97/45111, see urea derivatives of the general formula according to claim 1 (examples and page 14);
D7 : WO 01/12188, pyrazolyl substituted urea derivatives of general formula (I) which are anti-tumor agents (see pages 11 to 15).

inventive step

Irrespective of the fact that the present subject-matter is not novel, the following is already noted having regard to inventive step (art. 33(3) PCT): The present compounds according to general formula (I) are said to be chloride channel blockers as stated on eg page 29 of the application. At present however no biological data are available in

order to credibly support this alleged property. In support of inventive step versus the closest state of the art D1-D4, D6 and D7, biological data showing improved efficacy as chloride channel blockers are necessary. In particular, these data must be representative over the whole area as claimed.

industrial applicability

For the assessment of claim 20 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claim. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Further remarks:

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D5-D7 is not mentioned in the description, nor are these documents identified therein.